(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 July 2005 (21.07.2005)

PCT

(10) International Publication Number
WO 2005/066169 A2

(51) International Patent Classification[7]: C07D 471/00

(21) International Application Number:
PCT/US2004/043447

(22) International Filing Date:
23 December 2004 (23.12.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/533,465	30 December 2003 (30.12.2003)	US
60/555,936	24 March 2004 (24.03.2004)	US
60/581,335	18 June 2004 (18.06.2004)	US

(71) Applicant *(for all designated States except US)*: **3M INNOVATIVE PROPERTIES COMPANY** [US/US]; 3M Center, Post Office Box 33427, Saint Paul, Minnesota 55133-3427 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BONK, Jason D.**, [US/US]; Post Office Box 33427, Saint Paul, Minnesota 55133-3427 (US). **DELLARIA, Joseph F. Jr.**, [US/US]; Post Office Box 33427, Saint Paul, Minnesota 55133-3427 (US).

(74) Agents: **RINGSRED, Ted K.,** et al.; Office of Intellectual Property Counsel, Post Office Box 33427, Saint Paul, Minnesota 55133-3427 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: IMIDAZOQUINOLINYL, IMIDAZOPYRIDINYL, AND IMIDAZONAPHTHYRIDINYL SULFONAMIDES

(57) Abstract: Imidazoquinolinyl, imidazopyridinyl, and imidazonaphthyridinyl sulfonamide compounds, pharmaceutical compositions containing the compounds, intermediates, and methods of making and methods of use of these compounds as immunomodulators, for inducing cytokine biosynthesis in animals and in the treatment of diseases including viral and neoplastic diseases are disclosed.

WO 2005/066169 A2

IMIDAZOQUINOLINYL, IMIDAZOPYRIDINYL, AND IMIDAZONAPHTHYRIDINYL SULFONAMIDES

RELATED APPLICATIONS

The present invention claims priority to U.S. Provisional Application Serial No. 60/533465, filed December 30, 2003; U.S. Provisional Application Serial No. 60/555936, filed March 24, 2004; and U.S. Provisional Application Serial No. 60/581335, filed June 18, 2004, all of which are incorporated herein by reference.

FIELD OF THE INVENTION

This invention relates to derivatives of imidazoquinoline, imidazopyridine, and imidazonaphthyridine compounds and to pharmaceutical compositions containing the compounds. A further aspect of this invention relates to the use of these compounds as immunomodulators, for inducing cytokine biosynthesis in animals and in the treatment of diseases including viral and neoplastic diseases.

BACKGROUND OF THE INVENTION

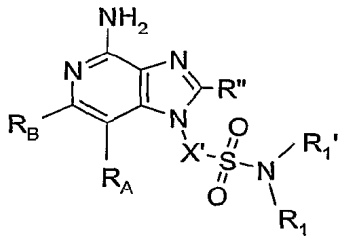
In the 1950's the 1*H*-imidazo[4,5-*c*]quinoline ring system was developed, and 1-(6-methoxy-8-quinolinyl)-2-methyl-1*H*-imidazo[4,5-*c*]quinoline was synthesized for possible use as an antimalarial agent. Subsequently, syntheses of various substituted 1*H*-imidazo[4,5-*c*] quinolines were reported. For example, 1-[2-(4-piperidyl)ethyl]-1*H*-imidazo[4,5-*c*]quinoline was synthesized as a possible anticonvulsant and cardiovascular agent. Also, several 2-oxoimidazo[4,5-*c*]quinolines have been reported.

Certain 1*H*-imidazo[4,5-*c*]quinolin-4-amines and 1- and 2-substituted derivatives thereof were later found to be useful as antiviral agents, bronchodilators and immunomodulators. Subsequently, certain substituted 1*H*-imidazo[4,5-*c*] pyridin-4-amine, quinolin-4-amine, tetrahydroquinolin-4-amine, naphthyridin-4-amine, and tetrahydronaphthyridin-4-amine compounds as well as certain analogous thiazolo and oxazolo compounds were synthesized and found to be useful as immune response modifiers, rendering them useful in the treatment of a variety of disorders.

There continues to be interest in and a need for compounds that have the ability to modulate the immune response, by induction of cytokine biosynthesis or other mechanisms.

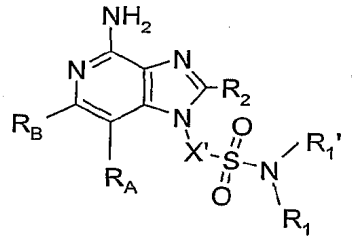
SUMMARY

The present invention provides a new class of compounds that are useful in inducing cytokine biosynthesis in animals. Such compounds are of the following Formula I:

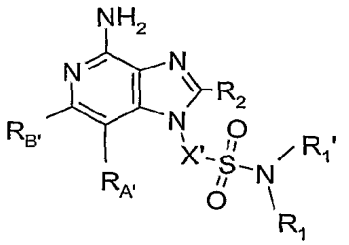


(I)

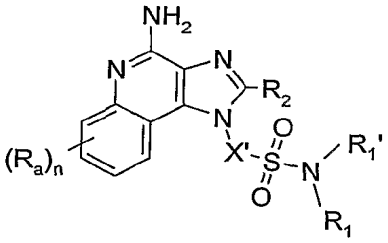
and more specifically, compounds of the following Formulas Ia, Ib, II, IIa, III, IV, V, VI, VII, VIII, IX, X, and XI:



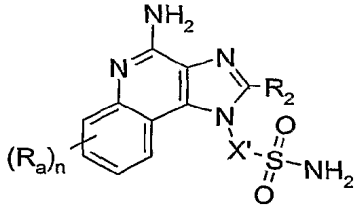
(Ia)



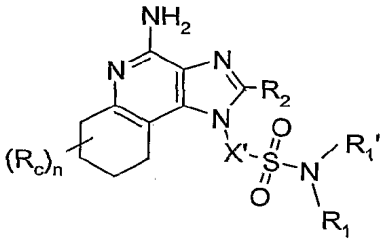
(Ib)



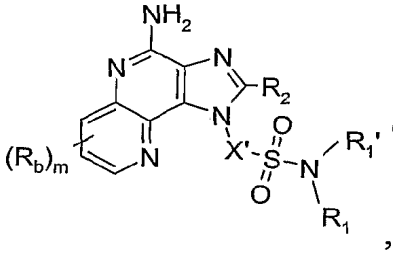
(II)



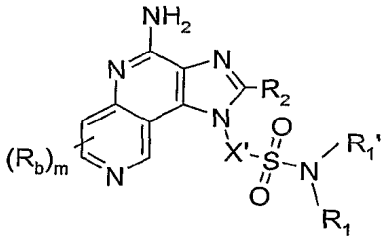
(IIa)



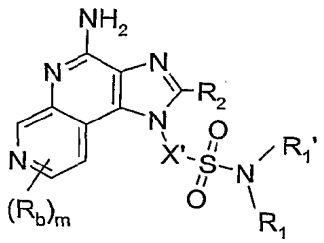
(III)



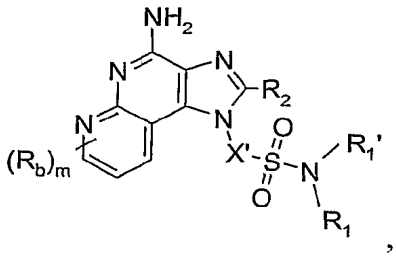
(IV)



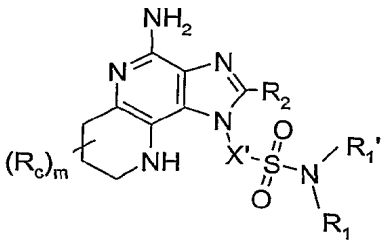
(V)



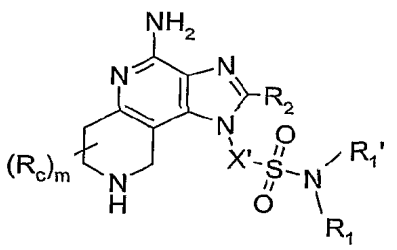
(VI)



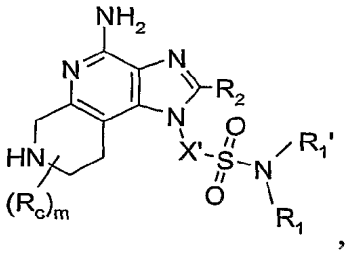
(VII)



(VIII)

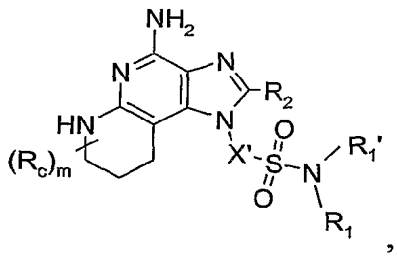


(IX)



, and

(X)



(XI)

wherein: R_1, R'', R_2, R_1', R_A, R_B, $R_{A'}$, $R_{B'}$, R_a, R_b, R_c, X', n, and m are as defined below; and pharmaceutically acceptable salts thereof.

The compounds of Formulas I, Ia, Ib, II, IIa, III, IV, V, VI, VII, VIII, IX, X, and XI are useful, for example, as immune response modifiers (IRMs) due to their ability to modulate cytokine biosynthesis (e.g., induce the biosynthesis or production of one or more cytokines) and otherwise modulate the immune response when administered to animals. Compounds can be tested, for example, using the test procedure described in the Examples Section. Compounds can be tested for induction of cytokine biosynthesis by incubating human PBMC in a culture with the compound(s) at a concentration range of 30 to 0.014 μM and analyzing for interferon (α) or tumor necrosis factor (α) in the culture supernatant. The ability to modulate cytokine biosynthesis, for example, induce the biosynthesis of one or more cytokines, makes the compounds useful in the treatment of a variety of conditions such as viral diseases and neoplastic diseases, that are responsive to such changes in the immune response.

In another aspect, the present invention provides pharmaceutical compositions containing the immune response modifier compounds, and methods of inducing cytokine biosynthesis in an animal, treating a viral disease in an animal, and treating a neoplastic disease in an animal by administering an effective amount of one or more compounds of

Formulas I, Ia, Ib, II, IIa, III, IV, V, VI, VII, VIII, IX, X, and XI and/or pharmaceutically acceptable salts thereof to the animal.

In another aspect, the invention provides methods of synthesizing compounds of the Formulas I, Ia, Ib, II, IIa, III, IV, V, VI, VII, VIII, IX, X, and XI and intermediates useful in the synthesis of these compounds.

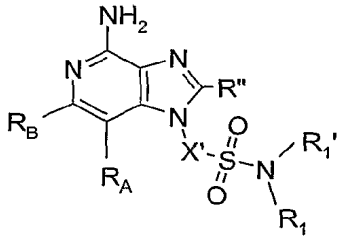
As used herein, "a," "an," "the," "at least one," and "one or more" are used interchangeably.

The terms "comprising" and variations thereof do not have a limiting meaning where these terms appear in the description and claims.

The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The description that follows more particularly exemplifies illustrative embodiments. Guidance is also provided herein through lists of examples, which can be used in various combinations. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.

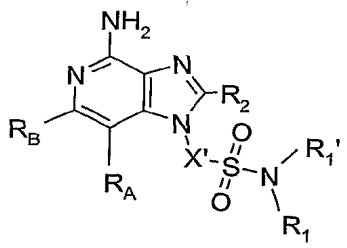
DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS OF THE INVENTION

The present invention provides compounds of the following Formula I:

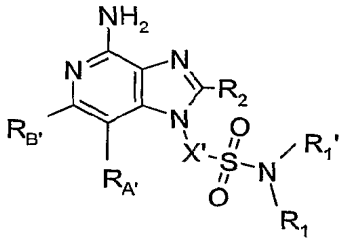


(I)

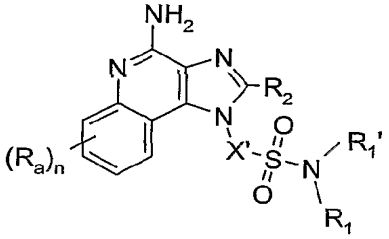
and more specifically, compounds of the following Formulas Ia, Ib, II, IIa, III, IV, V, VI, VII, VIII, IX, X, and XI:



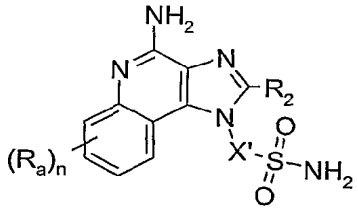
(Ia)



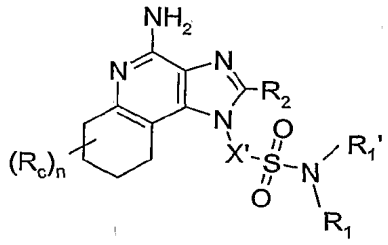
(Ib)



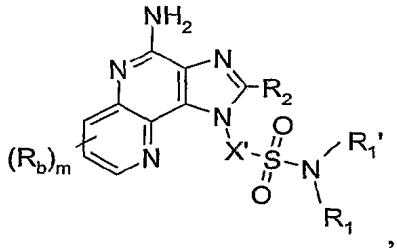
(II)



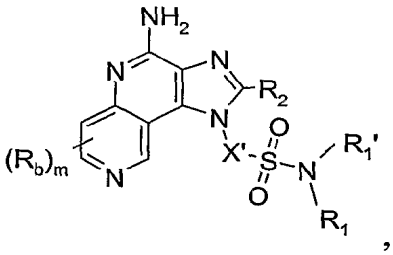
(IIa)



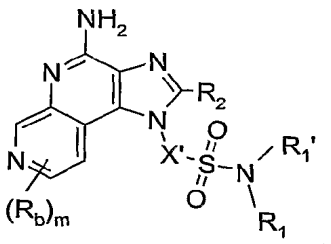
(III)



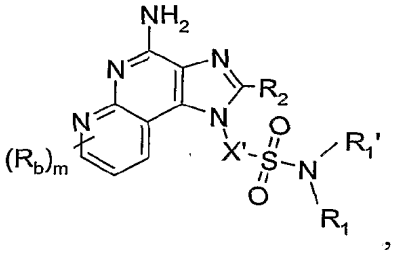
(IV)



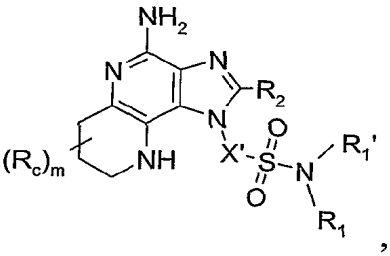
(V)



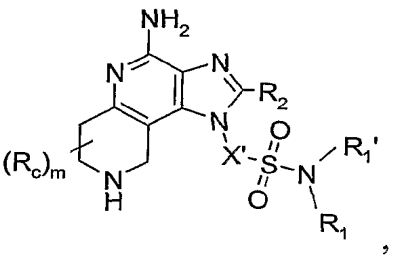
(VI)



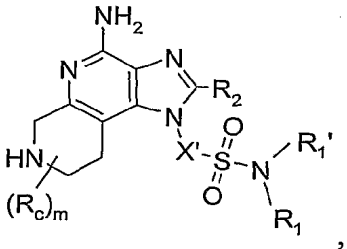
(VII)



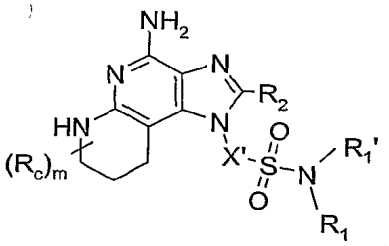
(VIII)



(IX)

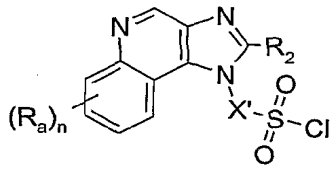


(X), and

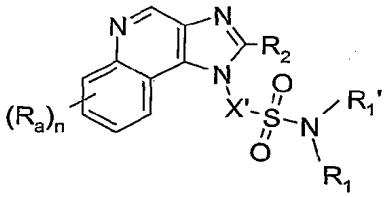


(XI)

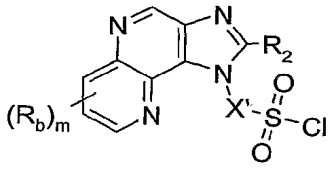
as well as intermediates of the following formulas XII, XIII, XIV, XV, XVI, and XVII:



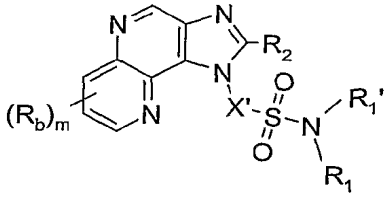
(XII)



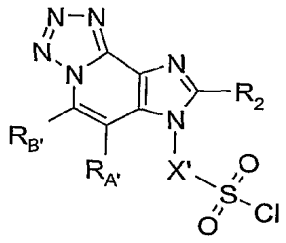
(XIII)



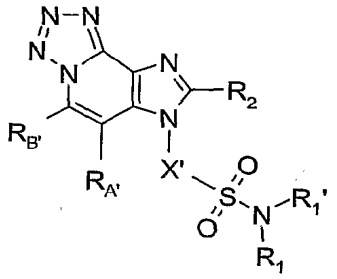
(XIV)



(XV)



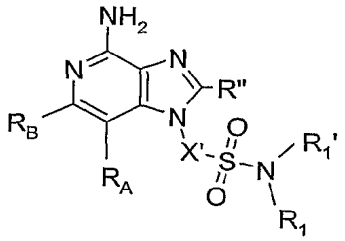
(XVI)



(XVII)

wherein: R_1, R'', R_2, R_1', R_A, R_B, $R_{A'}$, $R_{B'}$, R_a, R_b, R_c, X', n, and m are as defined below; and pharmaceutically acceptable salts thereof.

In one embodiment, the present invention provides compounds of the following Formula (I):



(I)

wherein:

X' is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene, and -CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1 and R_1' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

haloalkoxy,

halogen,

cyano,

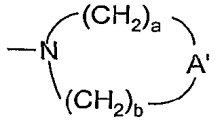
nitro,

arylsulfonyl,

alkylsulfonyl, and

$-N(R_9)_2$,

or R_1 and R_1' can join together to form a ring of the formula:



;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, $-N(R_4)-$, and $-N(Q-R_4)-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

Q is selected from the group consisting of a bond, -C(R_6)-, -C(R_6)-C(R_6)-, -S(O)$_2$-, -C(R_6)-N(R_8)-W-, -S(O)$_2$-N(R_8)-, -C(R_6)-O-, and -C(R_6)-N(OR_9)-;

W is selected from the group consisting of a bond, -C(O)-, and -S(O)$_2$-;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkylenyloxy, heteroaryl, heteroaryloxy, heteroarylalkylenyloxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkylenyloxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_6 is selected from the group consisting of =O and =S;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R'' is hydrogen or a non-interfering substituent;

R_A and R_B are independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

-N(R_9)$_2$;

or R_A and R_B taken together form either a fused aryl ring that is unsubstituted or substituted by one or more R_a groups, or a fused 5 to 7 membered saturated ring that is unsubstituted or substituted by one or more R_c groups;

or R_A and R_B taken together form a fused heteroaryl or 5 to 7 membered saturated ring, containing one heteroatom selected from the group consisting of N and S, wherein

the heteroaryl ring is unsubstituted or substituted by one or more R_b groups, and the 5 to 7 membered saturated ring is unsubstituted or substituted by one or more R_c groups;

R_a is selected from the group consisting of:

fluoro,

alkyl,

haloalkyl,

alkoxy, and

$-N(R_9)_2$;

R_b is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy, and

$-N(R_9)_2$; and

R_c is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

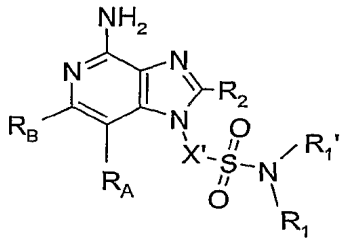
alkoxy,

alkylthio, and

$-N(R_9)_2$;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention also provides compounds of the following Formula (Ia):



(Ia)

wherein:

X' is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene, and -CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1 and R_1' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

haloalkoxy,

halogen,

cyano,

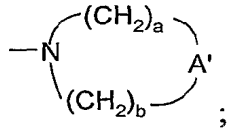
nitro,

arylsulfonyl,

alkylsulfonyl, and

$-N(R_9)_2$,

or R_1 and R_1' can join together to form a ring of the formula:



;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

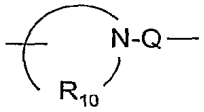
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

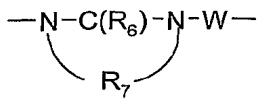
$-C(R_6)-N(R_8)-$,

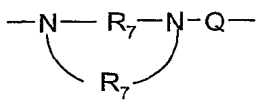
$-O-C(R_6)-N(R_8)-$,

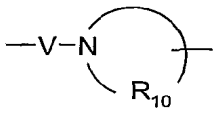
$-C(R_6)-N(OR_9)-$,

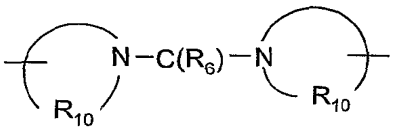


,


,

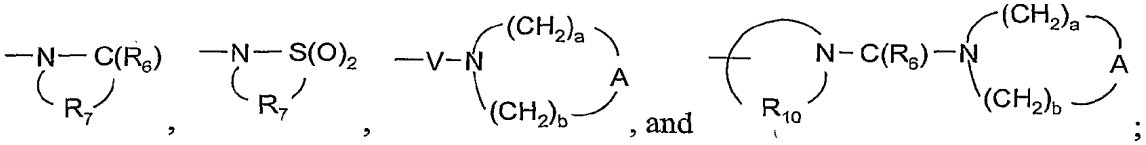

,


, and


;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkylenyloxy, heteroaryl, heteroaryloxy, heteroarylalkylenyloxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkylenyloxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:


;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, $-N(R_4)-$, and $-N(Q-R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

a and b are independently integers from 1 to 6 with the proviso that $a + b \leq 7$;

R_A and R_B are independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

or R_A and R_B taken together form either a fused aryl ring that is unsubstituted or substituted by one or more R_a groups, or a fused 5 to 7 membered saturated ring that is unsubstituted or substituted by one or more R_c groups;

or R_A and R_B taken together form a fused heteroaryl or 5 to 7 membered saturated ring, containing one heteroatom selected from the group consisting of N and S, wherein the heteroaryl ring is unsubstituted or substituted by one or more R_b groups, and the 5 to 7 membered saturated ring is unsubstituted or substituted by one or more R_c groups;

R_a is selected from the group consisting of:

fluoro,

alkyl,

haloalkyl,

alkoxy, and

$-N(R_9)_2$;

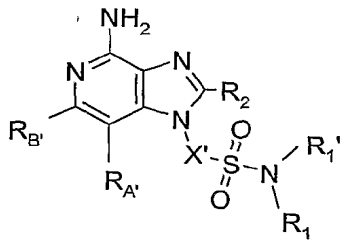
R_b is selected from the group consisting of:

halogen,
hydroxy,
alkyl,
alkenyl,
haloalkyl,
alkoxy, and
$-N(R_9)_2$; and

R_c is selected from the group consisting of:
halogen,
hydroxy,
alkyl,
alkenyl,
haloalkyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention also provides compounds of the following Formula (Ib):



(Ib)

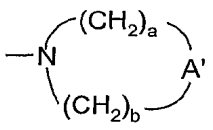
wherein:

X' is selected from the group consisting of $-CH(R_9)-$, $-CH(R_9)$-alkylene, and $-CH(R_9)$-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1 and R_1' are independently selected from the group consisting of:
hydrogen,

alkyl,
alkenyl,
aryl,
arylalkylenyl,
heteroaryl,
heteroarylalkylenyl,
heterocyclyl,
heterocyclylalkylenyl, and
alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:
hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
haloalkoxy,
halogen,
cyano,
nitro,
arylsulfonyl,
alkylsulfonyl, and
$-N(R_9)_2$,

or R_1 and R_1' can join together to form a ring of the formula:



;

R_2 is selected from the group consisting of:
$-R_4$,
$-X-R_4$,
$-X-Y-R_4$, and
$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_8)$-,

-$C(R_6)$-,

-$C(R_6)$-O-,

-O-$C(R_6)$-,

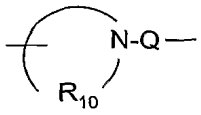
-O-C(O)-O-,

-$N(R_8)$-Q-,

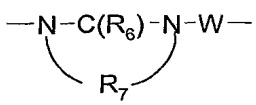
-$C(R_6)$-$N(R_8)$-,

-O-$C(R_6)$-$N(R_8)$-,

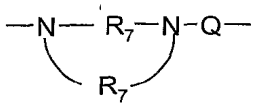
-$C(R_6)$-$N(OR_9)$-,



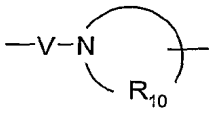
,



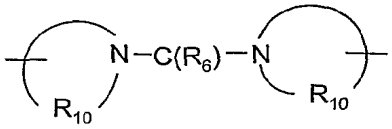
,



,



, and

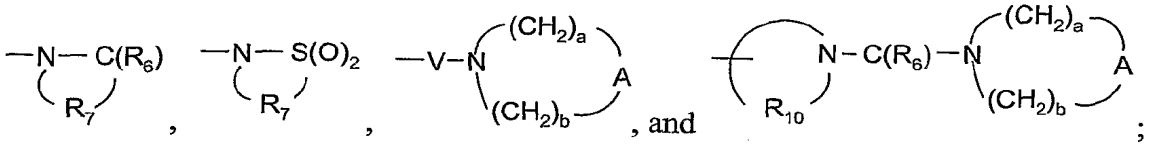


;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl,

alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkylenyloxy, heteroaryl, heteroaryloxy, heteroarylalkylenyloxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkylenyloxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, $-N(R_4)-$, and $-N(Q-R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7; and

$R_{A'}$ and $R_{B'}$ are independently selected from the group consisting of:

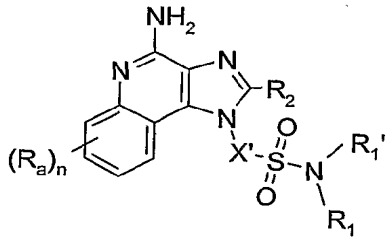
hydrogen,

halogen,

alkyl,
alkenyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention also provides compounds of the following Formula II:



(II)

wherein:

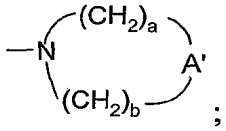
X' is selected from the group consisting of $-CH(R_9)-$, $-CH(R_9)$-alkylene, and $-CH(R_9)$-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1 and R_1' are independently selected from the group consisting of:

hydrogen,
alkyl,
alkenyl,
aryl,
arylalkylenyl,
heteroaryl,
heteroarylalkylenyl,
heterocyclyl,
heterocyclylalkylenyl, and
alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
haloalkoxy,
halogen,
cyano,
nitro,
arylsulfonyl,
alkylsulfonyl, and
$-N(R_9)_2$,

or R_1 and R_1' can join together to form a ring of the formula:



;

R_2 is selected from the group consisting of:

$-R_4$,
$-X-R_4$,
$-X-Y-R_4$, and
$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,
$-S(O)_{0-2}-$,
$-S(O)_2-N(R_8)-$,
$-C(R_6)-$,
$-C(R_6)-O-$,
$-O-C(R_6)-$,

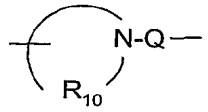
-O-C(O)-O-,

-N(R_8)-Q-,

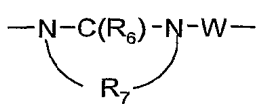
-C(R_6)-N(R_8)-,

-O-C(R_6)-N(R_8)-,

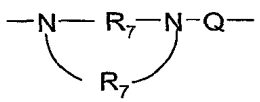
-C(R_6)-N(OR_9)-,



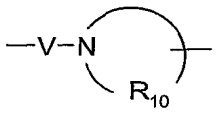
,



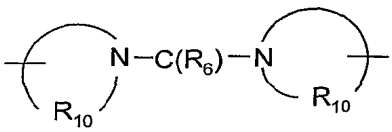
,



,



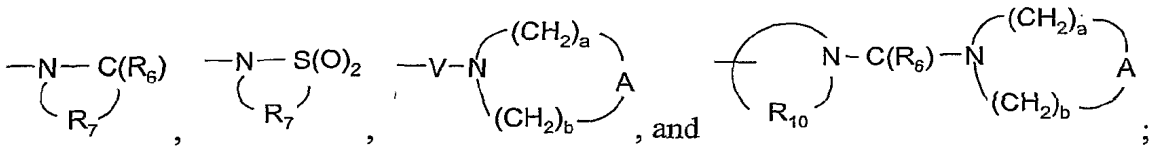
, and



;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkylenyloxy, heteroaryl, heteroaryloxy, heteroarylalkylenyloxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkylenyloxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, $-N(R_4)-$, and $-N(Q-R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

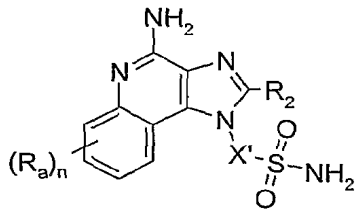
a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_a is selected from the group consisting of fluoro, alkyl, haloalkyl, alkoxy, and $-N(R_9)_2$; and

n is 0 to 4;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention also provides compounds of the following Formula IIa:



(IIa)

wherein:

X' is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene, and -CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_2 is selected from the group consisting of:

-R_4,

-X-R_4,

-X-Y-R_4, and

-X- R_5;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_8)$-,

-$C(R_6)$-,

-$C(R_6)$-O-,

-O-$C(R_6)$-,

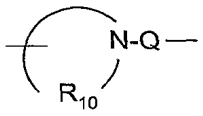
-O-C(O)-O-,

-$N(R_8)$-Q-,

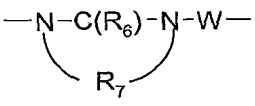
-$C(R_6)$-$N(R_8)$-,

-O-$C(R_6)$-$N(R_8)$-,

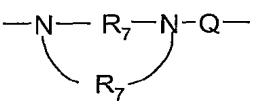
-$C(R_6)$-$N(OR_9)$-,



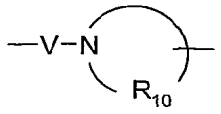
,



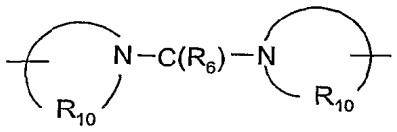
,



,



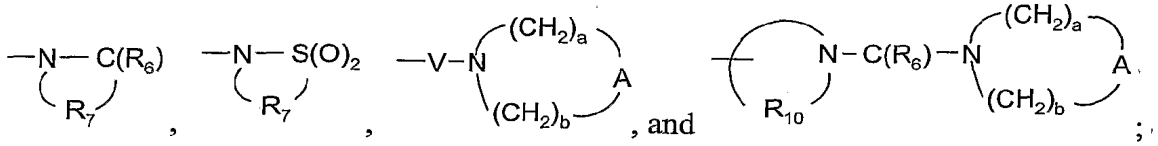
, and



;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkylenyloxy, heteroaryl, heteroaryloxy, heteroarylalkylenyloxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkylenyloxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



, , , and ;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and

$-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

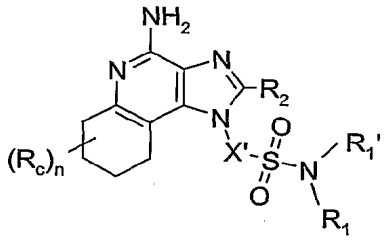
a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_a is selected from the group consisting of fluoro, alkyl, haloalkyl, alkoxy, and $-N(R_9)_2$; and

n is 0 to 4;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention also provides compounds of the following Formula III:



(III)

wherein:

X' is selected from the group consisting of $-CH(R_9)-$, $-CH(R_9)$-alkylene, and $-CH(R_9)$-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1 and R_1' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

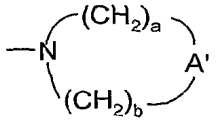
heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
haloalkoxy,
halogen,
cyano,
nitro,
arylsulfonyl,
alkylsulfonyl, and
$-N(R_9)_2$,

or R_1 and R_1' can join together to form a ring of the formula:



;

R_2 is selected from the group consisting of:

$-R_4$,
$-X-R_4$,
$-X-Y-R_4$, and
$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,
$-S(O)_{0-2}-$,
$-S(O)_2-N(R_8)-$,

-$C(R_6)$-,

-$C(R_6)$-O-,

-O-$C(R_6)$-,

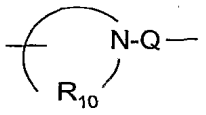
-O-C(O)-O-,

-$N(R_8)$-Q-,

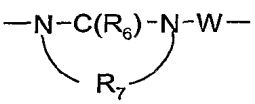
-$C(R_6)$-$N(R_8)$-,

-O-$C(R_6)$-$N(R_8)$-,

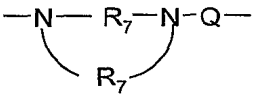
-$C(R_6)$-$N(OR_9)$-,



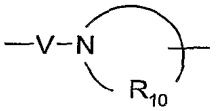
,



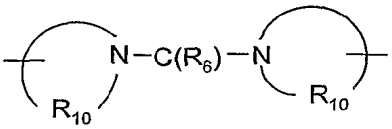
,



,



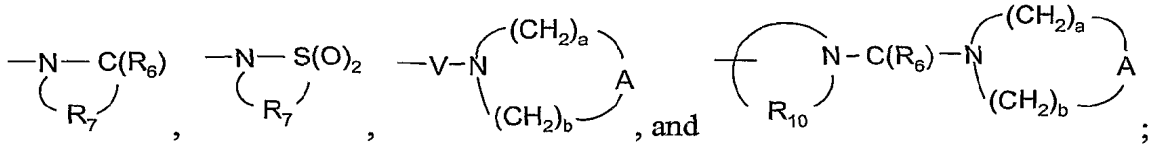
, and



;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkylenyloxy, heteroaryl, heteroaryloxy, heteroarylalkylenyloxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkylenyloxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, $-N(R_4)-$, and $-N(Q-R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

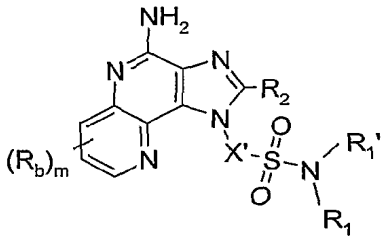
a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_c is selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; and

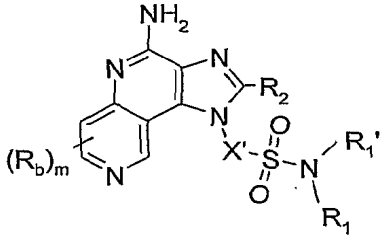
n is 0 to 4;

or a pharmaceutically acceptable salt thereof.

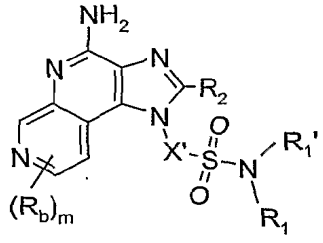
In other embodiments, the present invention also provides compounds of the following Formulas IV, V, VI, and VII:



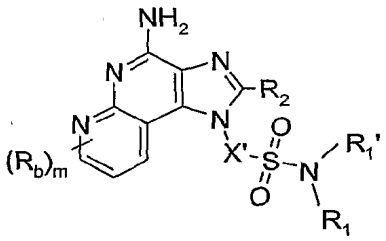
IV



V



VI, and



VII

wherein:

X' is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene, and -CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1 and R_1' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

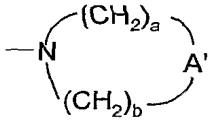
heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
haloalkoxy,
halogen,
cyano,
nitro,
arylsulfonyl,
alkylsulfonyl, and
$-N(R_9)_2$,

or R_1 and R_1' can join together to form a ring of the formula:



;

R_2 is selected from the group consisting of:

$-R_4$,
$-X-R_4$,
$-X-Y-R_4$, and
$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,
$-S(O)_{0-2}-$,
$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

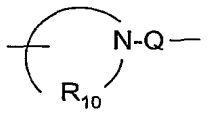
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

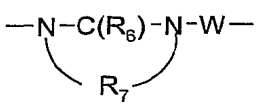
$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

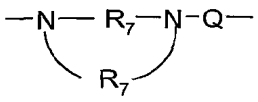
$-C(R_6)-N(OR_9)-$,



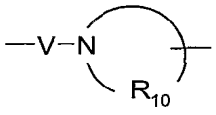
,



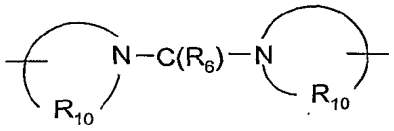
,



,



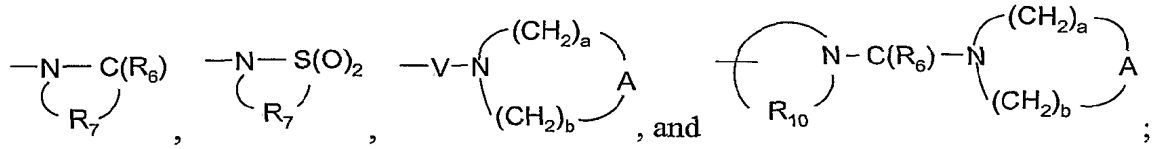
, and



;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkylenyloxy, heteroaryl, heteroaryloxy, heteroarylalkylenyloxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkylenyloxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, $-N(R_4)-$, and $-N(Q-R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

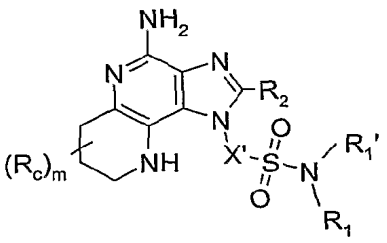
a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_b is selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, haloalkyl, alkoxy, and $-N(R_9)_2$; and

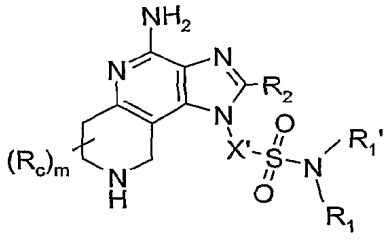
m is 0 to 3;

or a pharmaceutically acceptable salt thereof.

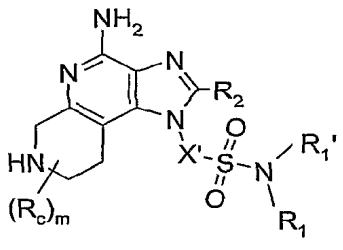
In other embodiments, the present invention also provides compounds of the following Formulas VIII, IX, X, and XI:



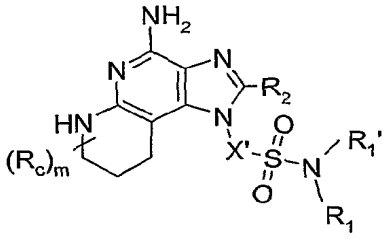
VIII



IX



X, and



XI

wherein:

X' is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene, and -CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1 and R_1' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

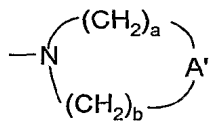
hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,
alkoxy,
haloalkoxy,
halogen,
cyano,
nitro,
arylsulfonyl,
alkylsulfonyl, and
$-N(R_9)_2$,

or R_1 and R_1' can join together to form a ring of the formula:



;

R_2 is selected from the group consisting of:

$-R_4$,
$-X-R_4$,
$-X-Y-R_4$, and
$-X-R_5$;

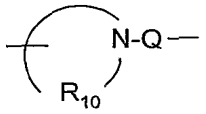
X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

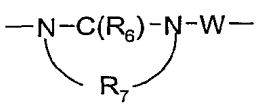
-O-,
$-S(O)_{0-2}-$,
$-S(O)_2-N(R_8)-$,
$-C(R_6)-$,
$-C(R_6)-O-$,
$-O-C(R_6)-$,
-O-C(O)-O-,
$-N(R_8)-Q-$,
$-C(R_6)-N(R_8)-$,

-O-C(R_6)-N(R_8)-,

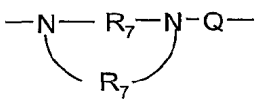
-C(R_6)-N(OR_9)-,



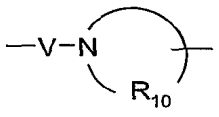
,



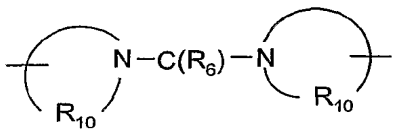
,



,



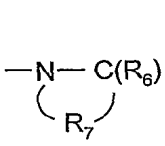
, and



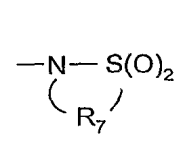
;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkylenyloxy, heteroaryl, heteroaryloxy, heteroarylalkylenyloxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkylenyloxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

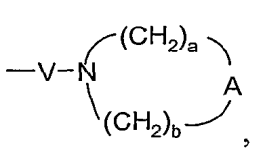
R_5 is selected from the group consisting of:



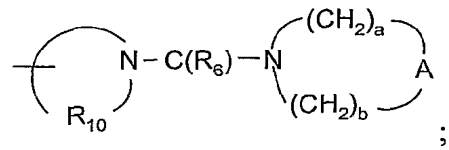
,



,



, and



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, $-N(R_4)-$, and $-N(Q-R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

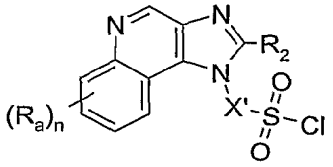
a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_c is selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; and

m is 0 to 3;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention also provides intermediate compounds of the following Formula XII:



(XII)

wherein:

X' is selected from the group consisting of $-CH(R_9)-$, $-CH(R_9)$-alkylene, and $-CH(R_9)$-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

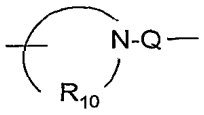
-O-C(O)-O-,

$-N(R_8)-Q-$,

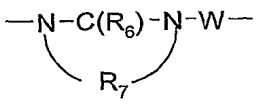
$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

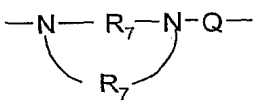
$-C(R_6)-N(OR_9)-$,



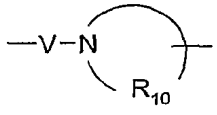
,



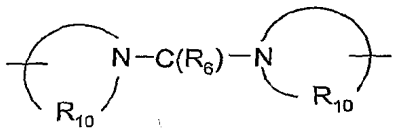
,



,



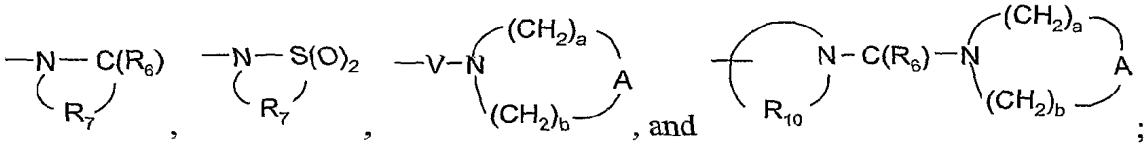
, and



;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkylenyloxy, heteroaryl, heteroaryloxy, heteroarylalkylenyloxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkylenyloxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

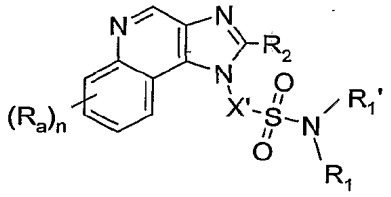
a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_a is selected from the group consisting of fluoro, alkyl, haloalkyl, alkoxy, and $-N(R_9)_2$; and

n is 0 to 4;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention also provides intermediate compounds of the following Formula XIII:



(XIII)

wherein:

X' is selected from the group consisting of $-CH(R_9)-$, $-CH(R_9)$-alkylene, and $-CH(R_9)$-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1 and R_1' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

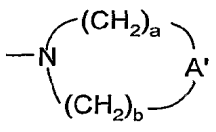
alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,
hydroxyalkyl,
alkoxy,
haloalkoxy,
halogen,
cyano,
nitro,
arylsulfonyl,
alkylsulfonyl, and
$-N(R_9)_2$,

or R_1 and R_1' can join together to form a ring of the formula:



;

R_2 is selected from the group consisting of:

$-R_4$,
$-X-R_4$,
$-X-Y-R_4$, and
$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

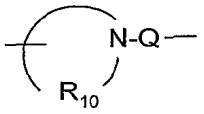
Y is selected from the group consisting of:

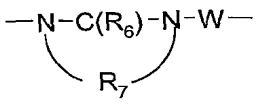
-O-,
$-S(O)_{0-2}-$,
$-S(O)_2-N(R_8)-$,
$-C(R_6)-$,
$-C(R_6)-O-$,
$-O-C(R_6)-$,
-O-C(O)-O-,
$-N(R_8)-Q-$,

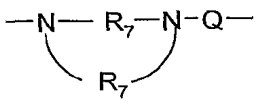
$-C(R_6)-N(R_8)-$,

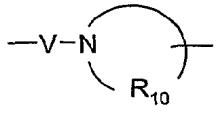
$-O-C(R_6)-N(R_8)-$,

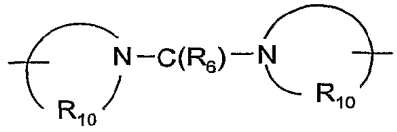
$-C(R_6)-N(OR_9)-$,


,


,

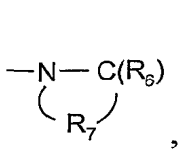
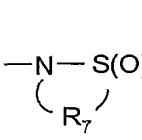
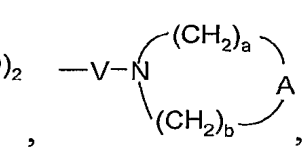
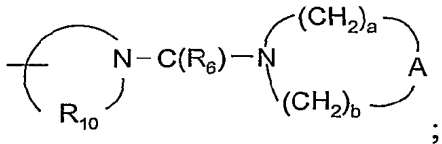

,


, and


;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkylenyloxy, heteroaryl, heteroaryloxy, heteroarylalkylenyloxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkylenyloxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:


,

,

, and

;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, $-N(R_4)-$, and $-N(Q-R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

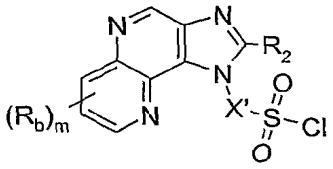
a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_a is selected from the group consisting of fluoro, alkyl, haloalkyl, alkoxy, and $-N(R_9)_2$; and

n is 0 to 4;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention also provides intermediate compounds of the following Formula XIV:



(XIV)

wherein:

X' is selected from the group consisting of $-CH(R_9)-$, $-CH(R_9)$-alkylene, and $-CH(R_9)$-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-O-$,

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

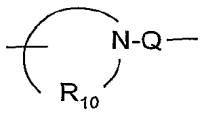
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

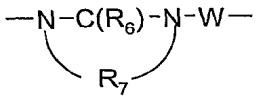
$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

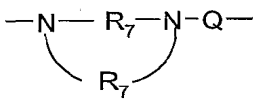
$-C(R_6)-N(OR_9)-$,



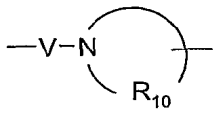
,



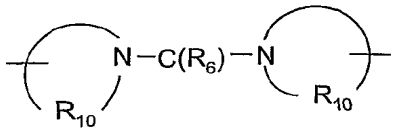
,



,



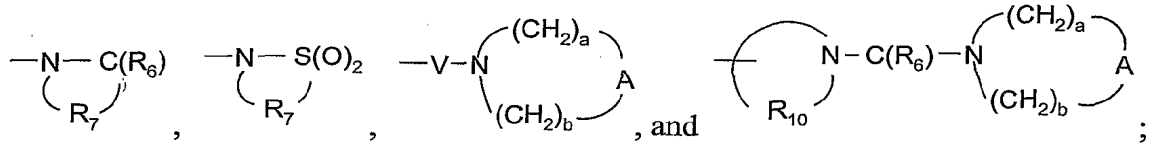
, and



;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkylenyloxy, heteroaryl, heteroaryloxy, heteroarylalkylenyloxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkylenyloxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

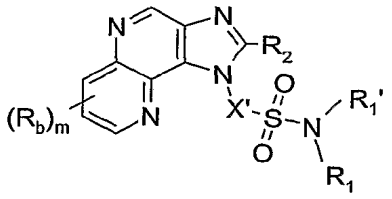
a and b are independently integers from 1 to 6 with the proviso that $a + b \leq 7$;

R_b is selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, haloalkyl, alkoxy, and $-N(R_9)_2$; and

m is 0 to 3;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention also provides intermediate compounds of the following Formula XV:



(XV)

wherein:

X' is selected from the group consisting of $-CH(R_9)-$, $-CH(R_9)$-alkylene, and $-CH(R_9)$-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1 and R_1' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

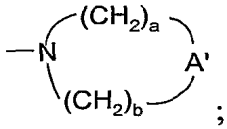
hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,
alkoxy,
haloalkoxy,
halogen,
cyano,
nitro,
arylsulfonyl,
alkylsulfonyl, and
$-N(R_9)_2$,

or R_1 and R_1' can join together to form a ring of the formula:



;

R_2 is selected from the group consisting of:

$-R_4$,
$-X-R_4$,
$-X-Y-R_4$, and
$-X-R_5$;

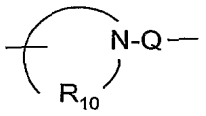
X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

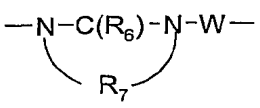
-O-,
$-S(O)_{0-2}-$,
$-S(O)_2-N(R_8)-$,
$-C(R_6)-$,
$-C(R_6)-O-$,
$-O-C(R_6)-$,
-O-C(O)-O-,
$-N(R_8)-Q-$,
$-C(R_6)-N(R_8)-$,

-O-C(R_6)-N(R_8)-,

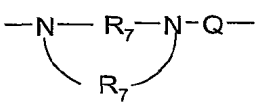
-C(R_6)-N(OR_9)-,



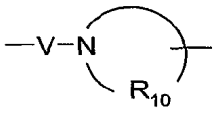
,



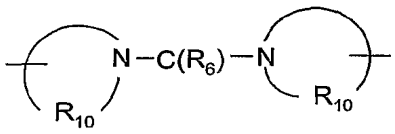
,



,



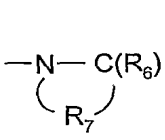
, and



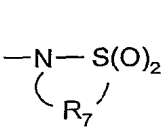
;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkylenyloxy, heteroaryl, heteroaryloxy, heteroarylalkylenyloxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkylenyloxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

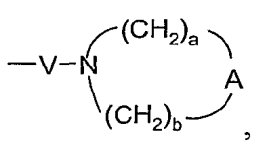
R_5 is selected from the group consisting of:



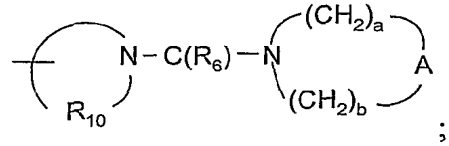
,



,



, and



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, $-N(R_4)-$, and $-N(Q-R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

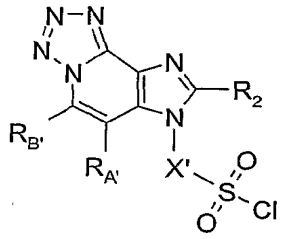
a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_b is selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, haloalkyl, alkoxy, and $-N(R_9)_2$; and

m is 0 to 3;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention also provides intermediate compounds of the following Formula XVI:



(XVI)

wherein:

X' is selected from the group consisting of $-CH(R_9)-$, $-CH(R_9)$-alkylene, and $-CH(R_9)$-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-O-$,

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

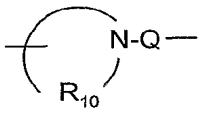
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

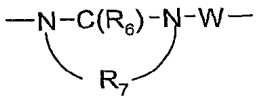
$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

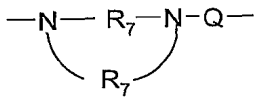
$-C(R_6)-N(OR_9)-$,



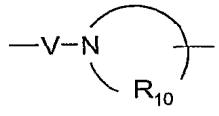
,



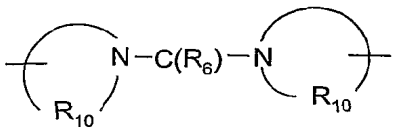
,



,



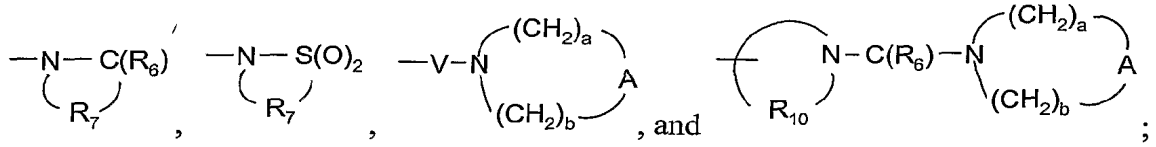
, and



;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkylenyloxy, heteroaryl, heteroaryloxy, heteroarylalkylenyloxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkylenyloxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

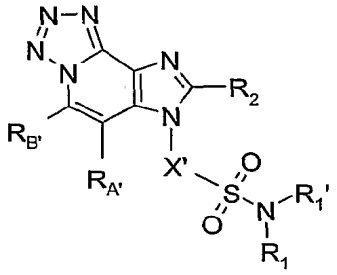
W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7; and

$R_{A'}$ and $R_{B'}$ are independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention also provides intermediate compounds of the Formula XVII:



(XVII)

wherein:

X' is selected from the group consisting of $-CH(R_9)-$, $-CH(R_9)$-alkylene, and $-CH(R_9)$-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1 and R_1' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

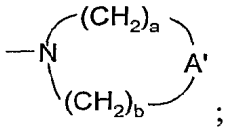
heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
haloalkoxy,
halogen,
cyano,
nitro,
arylsulfonyl,
alkylsulfonyl, and
$-N(R_9)_2$,

or R_1 and R_1' can join together to form a ring of the formula:



;

R_2 is selected from the group consisting of:

$-R_4$,
$-X-R_4$,
$-X-Y-R_4$, and
$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,
$-S(O)_{0-2}-$,
$-S(O)_2-N(R_8)-$,
$-C(R_6)-$,
$-C(R_6)-O-$,
$-O-C(R_6)-$,

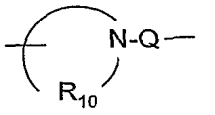
-O-C(O)-O-,

-N(R_8)-Q-,

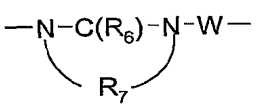
-C(R_6)-N(R_8)-,

-O-C(R_6)-N(R_8)-,

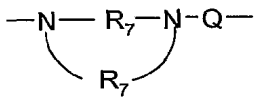
-C(R_6)-N(OR_9)-,



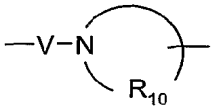
,



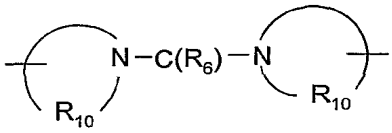
,



,



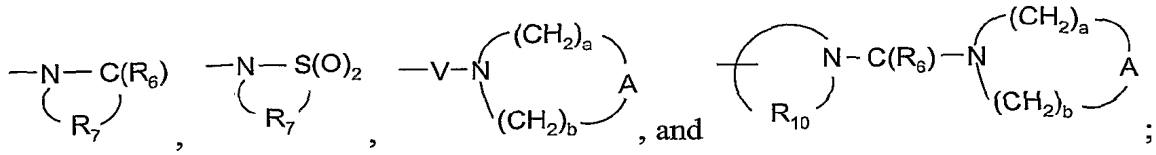
, and



;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkylenyloxy, heteroaryl, heteroaryloxy, heteroarylalkylenyloxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkylenyloxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, $-N(R_4)-$, and $-N(Q-R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

$R_{A'}$ and $R_{B'}$ are independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$;

or a pharmaceutically acceptable salt thereof.

As used herein, the terms "alkyl," "alkenyl," "alkynyl" and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups, i.e. cycloalkyl and cycloalkenyl. Unless otherwise specified, these groups contain from 1 to 20 carbon atoms, with alkenyl groups containing from 2 to 20 carbon atoms, and alkynyl groups containing from 2 to 20 carbon atoms. In some embodiments, these groups have a total of up to 10 carbon atoms, up to 8 carbon atoms, up to 6 carbon atoms, or up to 4 carbon atoms. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 10 ring carbon atoms. Exemplary cyclic groups include cyclopropyl,

cyclopropylmethyl, cyclopentyl, cyclohexyl, adamantyl, and substituted and unsubstituted bornyl, norbornyl, and norbornenyl.

Unless otherwise specified, "alkylene," "alkenylene," and "alkynylene" are the divalent forms of the "alkyl," "alkenyl," and "alkynyl" groups defined above. The terms, "alkylenyl," "alkenylenyl," and "alkynylenyl" are use when "alkylene," "alkenylene," and "alkynylene," respectively, are substituted. For example, an arylalkylenyl group comprises an alkylene moiety to which an aryl group is attached.

The term "haloalkyl" is inclusive of groups that are substituted by one or more halogen atoms, including perfluorinated groups. This is also true of other groups that include the prefix "halo-." Examples of suitable haloalkyl groups are chloromethyl, trifluoromethyl, and the like.

The term "aryl" as used herein includes carbocyclic aromatic rings or ring systems. Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl and indenyl.

Unless otherwise indicated, the term "heteroatom" refers to the atoms O, S, or N.

The term "heteroaryl" includes aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N). Suitable heteroaryl groups include furyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, triazolyl, pyrrolyl, tetrazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, benzofuranyl, benzothiophenyl, carbazolyl, benzoxazolyl, pyrimidinyl, benzimidazolyl, quinoxalinyl, benzothiazolyl, naphthyridinyl, isoxazolyl, isothiazolyl, purinyl, quinazolinyl, pyrazinyl, 1-oxidopyridyl, pyridazinyl, triazinyl, tetrazinyl, oxadiazolyl, thiadiazolyl, and so on.

The term "heterocyclyl" includes non-aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N) and includes all of the fully saturated and partially unsaturated derivatives of the above mentioned heteroaryl groups. Exemplary heterocyclic groups include pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, thiazolidinyl, imidazolidinyl, isothiazolidinyl, tetrahydropyranyl, quinuclidinyl, homopiperidinyl (azepanyl), homopiperazinyl (diazepanyl), 1,3-dioxolanyl, aziridinyl, dihydroisoquinolin-(1*H*)-yl, octahydroisoquinolin-(1*H*)-yl, dihydroquinolin-(2*H*)-yl, octahydroquinolin-(2*H*)-yl, dihydro-1*H*-imidazolyl, and the like. When "heterocyclyl" contains a nitrogen atom, the point of attachment of the heterocyclyl group may be the nitrogen atom.

The terms "arylene," "heteroarylene," and "heterocyclylene" are the divalent forms of the "aryl," "heteroaryl," and "heterocyclyl" groups defined above. The terms, "arylenyl," "heteroarylenyl," and "heterocyclylenyl" are used when "arylene," "heteroarylene," and "heterocyclylene," respectively, are substituted. For example, an alkylarylenyl group comprises an arylene moiety to which an alkyl group is attached.

The invention is inclusive of the compounds and salts thereof, described herein in any of their pharmaceutically acceptable forms, including isomers (e.g., diastereomers and enantiomers), solvates, polymorphs, and the like. In particular, if a compound is optically active, the invention specifically includes each of the compound's enantiomers as well as racemic mixtures of the enantiomers.

Herein, "non-interfering" means that the ability of the compound or salt, which includes a non-interfering substituent, to modulate (e.g., induce or inhibit) the biosynthesis of one or more cytokines is not destroyed by the non-interfering substitutent. For certain embodiments, R" is hydrogen or a non-interfering substituent. Illustrative non-interfering R" groups include those described herein for R_2.

When a group (or substituent or variable) is present more than once in any Formula described herein, each group (or substituent or variable) is independently selected, whether explicitly stated or not. For example, for the formula $-N(R_9)_2$ each R_9 group is independently selected. In another example, when an R_2 and an A' group both contain an R_4 group, each R_4 group is independently selected.

The invention is inclusive of the compounds described herein in any of their pharmaceutically acceptable forms, including isomers (e.g., diastereomers and enantiomers), salts, solvates, polymorphs, and the like. In particular, if a compound is optically active, the invention specifically includes each of the compound's enantiomers as well as racemic mixtures of the enantiomers. It should be understood that the term "compound" includes any or all of such forms, whether explicitly stated or not (although at times, "salts" are explicitly stated).

For any of the compounds presented herein, each one of the following variables (e.g., wherein: R_1, R", R_2, R_1', R_A, R_B, $R_{A'}$, $R_{B'}$, R_a, R_b, R_c, X', n, m, and so on) in any of its embodiments can be combined with any one or more of the other variables in any of their embodiments and associated with any one of the formulas described herein, as would

be understood by one of skill in the art. Each of the resulting combinations of variables is an embodiment of the present invention.

For certain embodiments, R" is hydrogen or a non-interfering substituent.

For certain embodiments, R_1 and R_1' are independently selected from the group consisting of: hydrogen, alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, heterocyclylalkylenyl, and alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of: hydroxy, alkyl, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, halogen, cyano, nitro, amino, alkylamino, dialkylamino, arylsulfonyl, and alkylsulfonyl.

For certain embodiments (particularly embodiments of Formulas I, Ia, Ib, II, III, IV, V, VI, VII, VIII, IX, X, and XI), R_1 and R_1' are independently selected from the group consisting of: hydrogen, alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, heterocyclylalkylenyl, and alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of: hydroxy, alkyl, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, halogen, cyano, nitro, arylsulfonyl, alkylsulfonyl, and $-N(R_9)_2$.

For certain embodiments (particularly embodiments of Formulas I, Ia, Ib, II, III, IV, V, VI, VII, VIII, IX, X, and XI), R_1 is selected from the group consisting of hydrogen, alkyl, aryl, substituted aryl, arylalkylenyl, substituted arylalkylenyl, and heteroaryl.

For certain embodiments (particularly embodiments of Formulas I, Ia, Ib, II, III, IV, V, VI, VII, VIII, IX, X, and XI), R_1 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, cyclohexyl, phenyl, 4-methoxyphenyl, benzyl, 4-methoxybenzyl, 2-pyridyl, and 3-pyridyl.

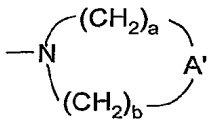
For certain embodiments (particularly embodiments of Formulas I, Ia, Ib, II, III, IV, V, VI, VII, VIII, IX, X, and XI), R_1 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, cyclohexyl, phenyl, 4-chlorophenyl, 4-fluorophenyl, 4-methoxyphenyl, benzyl, 4-methoxybenzyl, 2-pyridyl, and 3-pyridyl.

For certain embodiments (particularly embodiments of Formulas I, Ia, Ib, II, III, IV, V, VI, VII, VIII, IX, X, and XI), R_1 is selected from the group consisting of hydrogen, methyl, and isopropyl.

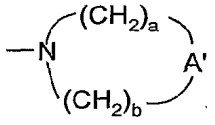
For certain embodiments (particularly embodiments of Formulas I, Ia, Ib, II, III, IV, V, VI, VII, VIII, IX, X, and XI), R_1' is hydrogen or alkyl.

For some embodiments (particularly embodiments of Formulas I, Ia, Ib, II, III, IV, V, VI, VII, VIII, IX, X, and XI), R_1' is hydrogen or methyl.

For certain embodiments, R_1 and R_1' can join together to form a ring of the formula:

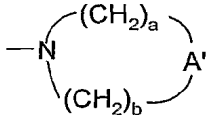


For certain embodiments, R_1 and R_1' can join together to form a ring of the formula:



wherein A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, $-N(R_4)-$, and $-N(Q-R_4)-$.

For certain embodiments (particularly embodiments of Formulas I, Ia, Ib, II, III, IV, V, VI, VII, VIII, IX, X, and XI), R_1 and R_1' can join together to form a ring of the formula:



wherein A' is selected from the group consisting of -O-, $-CH_2-$, $-NR_4-$, and $-N(Q-R_4)-$.

For certain embodiments (particularly embodiments of Formulas I, Ia, Ib, II, III, IV, V, VI, VII, VIII, IX, X, and XI), R_1 and R_1' join together to form a morpholine ring.

For certain embodiments (particularly embodiments of Formulas I, Ia, Ib, III, IV, V, VI, VII, VIII, IX, X, and XI), R_1 and R_1' are both hydrogen.

For certain embodiments, R_2 is selected from the group consisting of: $-R_4$, $-X-R_4$, $-X-Y-R_4$, and $-X-R_5$.

For certain embodiments (particularly embodiments of Formulas Ia, Ib, II, IIa, III, IV, V, VI, VII, VIII, IX, X, and XI), R_2 is selected from the group consisting of hydrogen, alkoxyalkylenyl, $-R_4$, $-X-R_4$, and $-X-Y-R_4$.

For certain embodiments (particularly embodiments of Formulas Ia, Ib, II, IIa, III, IV, V, VI, VII, VIII, IX, X, and XI) , R_2 is selected from the group consisting of hydrogen, alkoxyalkylenyl, hydroxyalkylenyl, $-R_4$, $-X-R_4$, and $-X-Y-R_4$.

For certain embodiments (particularly embodiments of Formulas Ia, Ib, II, IIa, III, IV, V, VI, VII, VIII, IX, X, and XI), R_2 is selected from the group consisting of hydrogen, alkoxyalkylenyl, $-R_4$, $-X-R_4$, and $-X-Y-R_4$, wherein X is C_{1-2} alkyl; Y is $-S(O)_{0-2}-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-$, $-C(R_6)-O-$, $-O-C(R_6)-$, $-O-C(O)-O-$, $-N(R_8)-Q-$, $-C(R_6)-N(R_8)-$, $-O-C(R_6)-N(R_8)-$, or $-C(R_6)-N(OR_9)-$; and R_4 is alkyl.

For certain embodiments (particularly embodiments of Formulas Ia, Ib, II, IIa, III, IV, V, VI, VII, VIII, IX, X, and XI), R_2 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, and $-X-R_4$ and $-X-Y-R_4$, wherein X is C_{1-2} alkyl; Y is $-S(O)_{0-2}-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-$, $-C(R_6)-O-$, $-O-C(R_6)-$, $-O-C(O)-O-$, $-N(R_8)-Q-$, $-C(R_6)-N(R_8)-$, $-O-C(R_6)-N(R_8)-$, or $-C(R_6)-N(OR_9)-$; and R_4 is alkyl.

For certain embodiments (particularly embodiments of Formulas Ia, Ib, II, IIa, III, IV, V, VI, VII, VIII, IX, X, and XI), R_2 is selected from the group consisting of hydrogen, C_{1-4} alkyl, C_{1-4} alkyl-O-C_{1-4} alkylenyl, and HO-C_{1-3} alkylenyl.

For certain embodiments (particularly embodiments of Formulas Ia, Ib, II, IIa, III, IV, V, VI, VII, VIII, IX, X, and XI), R_2 is selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{1-4} alkyl-O-C_{1-4} alkylenyl.

For certain embodiments, R_2 is selected from the group consisting of hydrogen, alkyl, and alkoxyalkylenyl.

For certain embodiments, R_2 is selected from the group consisting of hydrogen, methyl, ethyl, *n*-propyl, *n*-butyl, hydroxymethyl, 2-hydroxyethyl, ethoxymethyl, and 2-methoxyethyl.

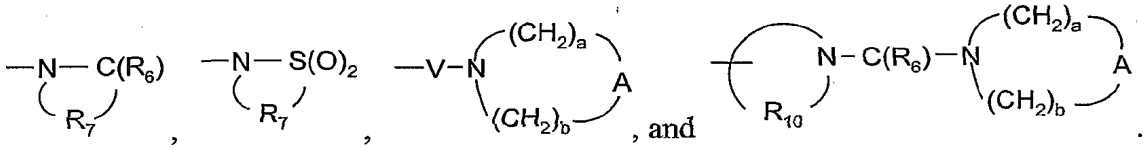
For certain embodiments, R_2 is selected from the group consisting of methyl, ethyl, *n*-propyl, *n*-butyl, hydroxymethyl, 2-hydroxyethyl, ethoxymethyl, and 2-methoxyethyl.

For certain embodiments, R_2 is selected from the group consisting of methyl, ethyl, propyl, butyl, ethoxymethyl, and 2-methoxyethyl.

For certain embodiments, R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and hetero\yclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkylenyloxy, heteroaryl, heteroaryloxy, heteroarylalkylenyloxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkylenyloxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo.

For certain embodiments (particularly embodiments of Formulas Ia, Ib, II, IIa, III, IV, V, VI, VII, VIII, IX, X, and XI), R_4 is alkyl.

For certain embodiments, R_5 is selected from the group consisting of:



, , , and .

For certain embodiments, R_6 is selected from the group consisting of =O and =S.

For certain embodiments, R_7 is C_{2-7} alkylene.

For certain embodiments, R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl.

For certain embodiments, R_9 is selected from the group consisting of hydrogen and alkyl.

For certain embodiments, R_{10} is C_{3-8} alkylene.

For certain embodiments, R_A and R_B are independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$.

For certain embodiments, R_A and R_B taken together form either a fused aryl ring that is unsubstituted or substituted by one or more R_a groups, or a fused 5 to 7 membered saturated ring that is unsubstituted or substituted by one or more R_c groups.

For certain embodiments, R_A and R_B taken together form a fused heteroaryl or 5 to 7 membered saturated ring, containing one heteroatom selected from the group consisting of N and S, wherein the heteroaryl ring is unsubstituted or substituted by one or more R_b

groups, and the 5 to 7 membered saturated ring is unsubstituted or substituted by one or more R_c groups.

For certain embodiments, R_A and R_B are independently selected from the group consisting of hydrogen and C_{1-4} alkyl.

For certain embodiments, $R_{A'}$ and $R_{B'}$ are independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$.

For certain embodiments, $R_{A'}$ and $R_{B'}$ are independently selected from the group consisting of hydrogen and C_{1-4} alkyl.

For certain embodiments, $R_{A'}$ and $R_{B'}$ are both methyl.

For certain embodiments, R_a is selected from the group consisting of alkyl, alkoxy, hydroxy, fluoro, trifluoromethyl, amino, alkylamino, and dialkylamino.

For certain embodiments, R_a is selected from the group consisting of fluoro, alkyl, haloalkyl, alkoxy, and $-N(R_9)_2$.

For certain embodiments, R_b is selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, haloalkyl, alkoxy, and $-N(R_9)_2$.

For certain embodiments, R_c is selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, haloalkyl, alkoxy, alkylthio, amino, alkylamino, and dialkylamino.

For certain embodiments, R_c is selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$.

For certain embodiments, A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$.

For certain embodiments, A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, $-N(R_4)-$, and $-N(Q-R_4)-$.

For certain embodiments, A' is selected from the group consisting of -O-, $-CH_2-$, $-N(R_4)-$, and $-N(Q-R_4)-$.

For certain embodiments, Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$.

For certain embodiments, V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$.

For certain embodiments, W is selected from the group consisting of a bond, -C(O)-, and -$S(O)_2$-.

For certain embodiments, X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups.

For certain embodiment (particularly embodiments of Formulas Ia, Ib, II, IIa, III, IV, V, VI, VII, VIII, IX, X, and XI), X is C_{1-2} alkylene.

For certain embodiments, X' is selected from the group consisting of -$CH(R_9)$-, -$CH(R_9)$-alkylene, and -$CH(R_9)$-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups.

For certain embodiments, X' is alkylene or alkenylene each of which may be optionally interrupted by one or more -O- groups.

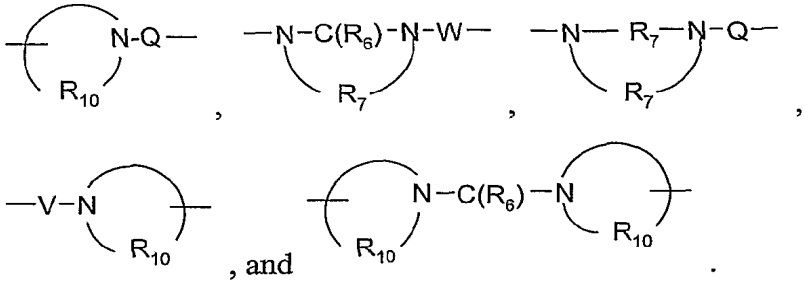
For certain embodiments (particularly embodiments of Formulas I, Ia, Ib, II, III, IV, V, VI, VII, VIII, IX, X, and XI), X' is -$(CH_2)_{2-4}$-O-$(CH_2)_{2-4}$-.

For certain embodiments (particularly embodiments of Formulas I, Ia, Ib, II, III, IV, V, VI, VII, VIII, IX, X, and XI), X' is -$(CH_2)_{1-7}$-.

For certain embodiments (particularly embodiments of Formulas I, Ia, Ib, II, III, IV, V, VI, VII, VIII, IX, X, and XI), X' is -$(CH_2)_2$-, -$(CH_2)_3$-, -$(CH_2)_4$-, -$(CH_2)_5$-, or -$CH_2C(CH_3)_2CH_2$-.

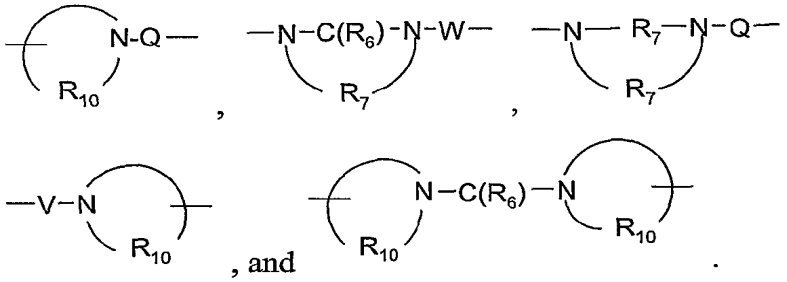
For certain embodiments (particularly embodiments of Formulas I, Ia, Ib, II, III, IV, V, VI, VII, VIII, IX, X, and XI), X' is -(CH_2)-$C(CH_3)_2$-.

For certain embodiments, Y is selected from the group consisting of: -O-, -$S(O)_{0-2}$-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-, -$C(R_6)$-O-, -O-$C(R_6)$-, -O-C(O)-O-, -$N(R_8)$-Q-, -$C(R_6)$-$N(R_8)$-, -O-$C(R_6)$-$N(R_8)$-, -$C(R_6)$-$N(OR_9)$-,



, and .

For certain embodiments, Y is selected from the group consisting of: -$S(O)_{0-2}$-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-, -$C(R_6)$-O-, -O-$C(R_6)$-, -O-C(O)-O-, -$N(R_8)$-Q-, -$C(R_6)$-$N(R_8)$-, -O-$C(R_6)$-$N(R_8)$-, -$C(R_6)$-$N(OR_9)$-,



, and .

For certain embodiment (particularly embodiments of Formulas Ia, Ib, II, IIa, III, IV, V, VI, VII, VIII, IX, X, and XI), Y is -$S(O)_{0-2}$-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-, -$C(R_6)$-O-, -O-$C(R_6)$-, -O-C(O)-O-, -$N(R_8)$-Q-, -$C(R_6)$-$N(R_8)$-, -O-$C(R_6)$-$N(R_8)$-, or -$C(R_6)$-$N(OR_9)$-.

For certain embodiments, a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7.

For certain embodiments, m is 0 to 3. For certain embodiments (particularly embodiments of Formulas IV, V, VI, VII, VIII, IX, X, and XI), m is 0.

For certain embodiments, n is 0 to 4. For certain embodiments, n is 0 to 3. For certain embodiments (particularly embodiments of Formulas II, IIa, and III), n is 0.

For certain embodiments (particularly embodiments of Formulas I, Ia, Ib, II, III, IV, V, VI, VII, VIII, IX, X, and XI), R_1' is hydrogen or alkyl, and R_1 is selected from the group consisting of hydrogen, alkyl, aryl, substituted aryl, arylalkylenyl, substituted arylalkylenyl, and heteroaryl.

For some embodiments (particularly embodiments of Formulas I, Ia, Ib, II, III, IV, V, VI, VII, VIII, IX, X, and XI), R_1' is hydrogen or methyl, and R_1 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, cyclohexyl, phenyl, 4-chlorophenyl, 4-fluorophenyl, 4-methoxyphenyl, benzyl, 4-methoxybenzyl, 2-pyridyl, and 3-pyridyl.

For some embodiments (particularly embodiments of Formulas I, Ia, Ib, II, III, IV, V, VI, VII, VIII, IX, X, and XI), R_1' is hydrogen or methyl, and R_1 is selected from the

group consisting of hydrogen, methyl, ethyl, propyl, butyl, cyclohexyl, phenyl, 4-methoxyphenyl, benzyl, 4-methoxybenzyl, 2-pyridyl, and 3-pyridyl.

Preparation of the Compounds

Compounds of the invention can be prepared according to Reaction Scheme I, wherein R_a, R_1, R_1', R_2, X', and n are as defined above.

In step (1) of Reaction Scheme I, an amine of Formula HO-X'-NH_2 is added to a 4-chloro-3-nitroquinoline of Formula XX to provide a hydroxy-substituted 3-nitroquinolin-4-amine of Formula XXI. The reaction is conveniently carried out by combining an amine of Formula HO-X'-NH_2 with a quinoline of Formula XX in the presence of a base such as triethylamine in a suitable solvent such as dichloromethane. The reaction can be carried out at ambient temperature, and the product can be isolated using conventional methods. Some amines of Formula HO-X'-NH_2, such as 4-aminobutanol, are commercially available; others can be prepared by known synthetic methods. Compounds of Formula XX are known and can be prepared according to known methods. See, for example, U.S. Patent Nos. 4,689,338; 4,929,624; 5,268,376; 5,346,905; 5,389,640; and 5,756,747.

In step (2) of Reaction Scheme I, the hydroxy group of a 3-nitroquinolin-4-amine of Formula XXI is chlorinated using conventional methods to provide a 3-nitroquinolin-4-amine of Formula XXII. The chlorination is conveniently carried out by adding thionyl chloride to a solution of the 3-nitroquinolin-4-amine of Formula XXI in a suitable solvent such as dichloromethane. The reaction can be carried out at sub-ambient temperatures, such as 0°C, or at ambient temperature, and the product can be isolated using conventional methods.

In step (3) of Reaction Scheme I, a 3-nitroquinolin-4-amine of Formula XXII is reduced to provide a quinoline-3,4-diamine of Formula XXIII. The reduction of the nitro group is conveniently carried out by adding an aqueous solution of sodium dithionite to a 3-nitroquinolin-4-amine of Formula XXII in a suitable solvent such as ethanol or a mixture of acetonitrile and ethanol. The reaction can be carried out at ambient temperature, and the product can be isolated by conventional methods.

Alternatively, step (3) can be carried out by hydrogenation in the presence of a heterogeneous hydrogenation catalyst, such as palladium on carbon or platinum on carbon. The reaction can be conveniently carried out on a Parr apparatus in a suitable solvent such

as acetonitrile, ethyl acetate, toluene, or ethanol. The product can be isolated by conventional methods.

In step (4) of Reaction Scheme I, a quinoline-3,4-diamine of Formula XXIII is treated with a carboxylic acid equivalent to provide a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXIV. Suitable carboxylic acid equivalents include orthoesters of Formula $R_2C(O\text{-alkyl})_3$, 1,1-dialkoxyalkyl alkanoates of Formula $R_2C(O\text{-alkyl})_2(O\text{-}C(O)\text{-alkyl})$, and acid chlorides of Formula $R_2C(O)Cl$. The selection of the carboxylic acid equivalent is determined by the desired substituent at R_2. For example, triethyl orthopropionate will provide a compound where R_2 is ethyl, and trimethyl orthovalerate will provide a compound where R_2 is a butyl group. The reaction is conveniently carried out by adding the carboxylic acid equivalent to a quinoline-3,4-diamine of Formula XXIII in a suitable solvent such as toluene or pyridine. Optionally, catalytic pyridine hydrochloride can be added. The reaction is carried out at a temperature high enough to drive off alcohol or water formed during the reaction, for example, at the reflux temperature of the solvent.

Alternatively, step (4) can be carried out in two steps when an acid chloride of Formula $R_2C(O)Cl$ is used as the carboxylic acid equivalent. Part (i) of step (4) is conveniently carried out by adding the acid chloride to a solution of a quinoline-3,4-diamine of Formula XXIII in a suitable solvent such as dichloromethane or acetonitrile to afford an amide. Optionally, a tertiary amine such as triethylamine, pyridine, or 4-dimethylaminopyridine can be added. The reaction can be carried out at ambient temperature or at a sub-ambient temperature, such as 0 °C. The amide product can be isolated and optionally purified using conventional techniques. Part (ii) of step (4) involves heating the amide prepared in part (i) to provide a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXIV. The reaction is conveniently carried out in a suitable solvent such as toluene at a temperature sufficient to drive off water formed during the reaction. The reaction can also be carried out in a solvent such as ethanol or methanol in the presence of a base such as aqueous sodium hydroxide. The product can be isolated using conventional methods.

In step (5) of Reaction Scheme I, the chloro group of a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXIV is displaced with potassium thioacetate to provide a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXV. The reaction is conveniently carried out by adding potassium thioacetate to a solution of a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXIV in a

suitable solvent such as *N,N*-dimethylformamide. The reaction can be carried out at ambient temperature, and the product can be isolated using conventional methods.

In step (6) of Reaction Scheme I, the thioacetate group of a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXV is hydrolyzed under basic conditions to provide a thiol-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula XXVI. The reaction is conveniently carried out by adding a solution of sodium methoxide in methanol to a solution of a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXV in methanol. The reaction can be carried out at ambient temperature, and the product can be isolated using conventional methods.

In step (7) of Reaction Scheme I, the thiol group of a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXVI is oxidized to a sulfonyl chloride of Formula XII. The reaction is conveniently carried out by adding a solution of sodium chlorate in a suitable solvent such as water to a solution of a thiol-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula XXVI in hydrochloric acid. The reaction can be carried out at a sub-ambient temperature such as 0 °C, and the product can be isolated using conventional methods.

In step (8) of Reaction Scheme I, the sulfonyl chloride of Formula XII is treated with an amine or an amine salt to provide a sulfonamide of Formula XIII. The reaction is conveniently carried out by adding an amine of Formula $NH(R_1)(R_1')$ to a sulfonyl chloride of Formula XII in a suitable solvent such as dichloromethane or pyridine. The reaction can be carried out at ambient temperature, and the product can be isolated using conventional methods.

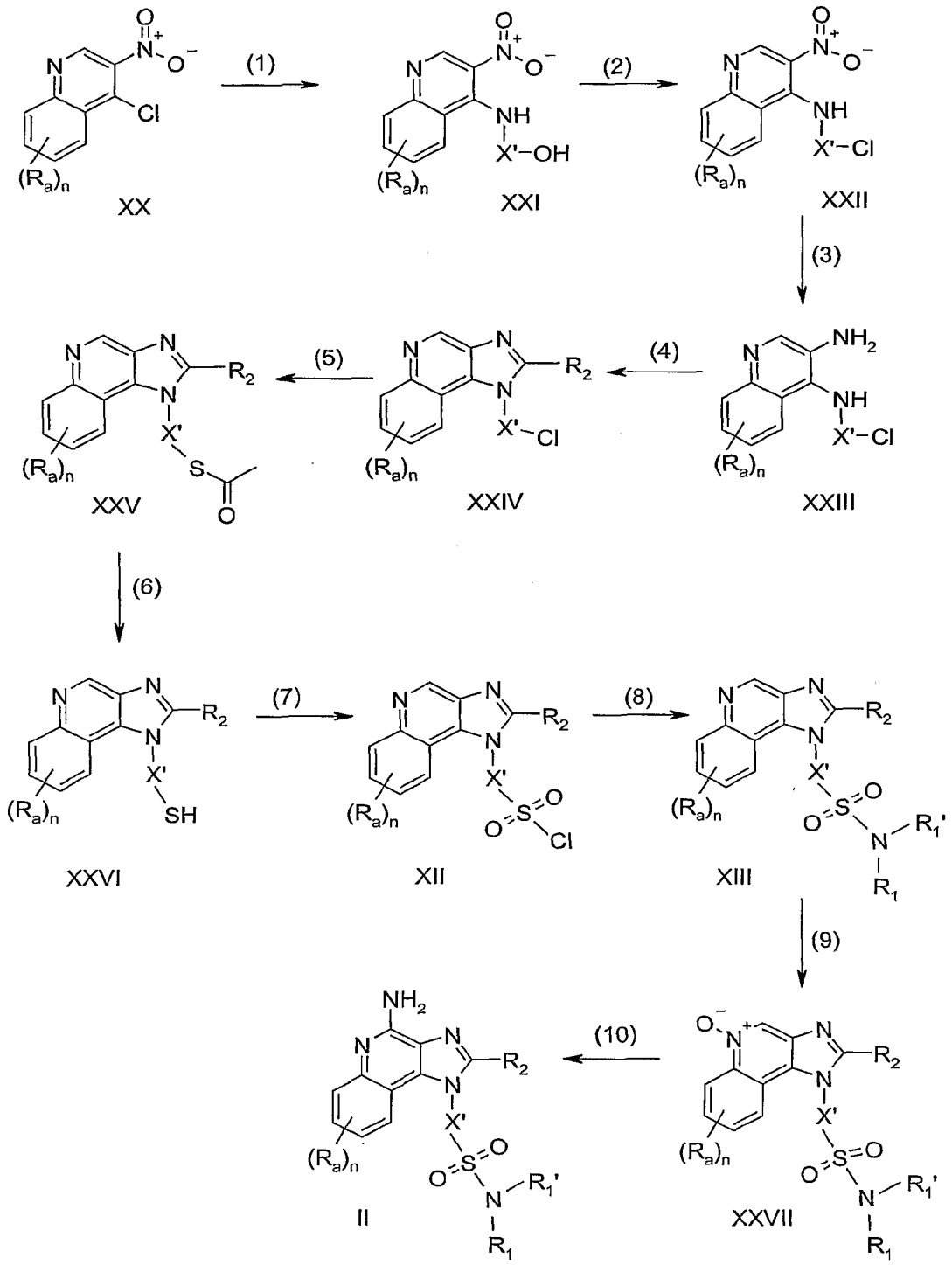
Alternatively, step (8) can be carried out by adding an amine hydrochloride of Formula $(R_1)(R_1')NH{\cdot}HCl$ followed by aqueous potassium carbonate to a solution of a sulfonyl chloride of Formula XII in a suitable solvent such as dichloromethane. The reaction can be carried out at ambient temperature, and the product can be isolated using conventional methods.

In step (9) of Reaction Scheme I, a 1*H*-imidazo[4,5-*c*]quinoline of Formula XIII is oxidized to provide a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula XXVII using a conventional oxidizing agent capable of forming *N*-oxides. The reaction is conveniently carried out by adding 3-chloroperoxybenzoic acid to a compound of Formula XIII in a solvent such as dichloromethane or chloroform. The reaction can be carried out at ambient temperature, and the product can be isolated using conventional methods.

In step (10) of Reaction Scheme I, a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula XXVII is aminated to provide a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula II. Step (10) can be carried out by the activation of an *N*-oxide of Formula XXVII by conversion to an ester and then reacting the ester with an aminating agent. Suitable activating agents include alkyl- or arylsulfonyl chlorides such as benzenesulfonyl chloride, methanesulfonyl chloride, or *p*-toluenesulfonyl chloride. Suitable aminating agents include ammonia, in the form of ammonium hydroxide, for example, and ammonium salts such as ammonium carbonate, ammonium bicarbonate, and ammonium phosphate. The reaction is conveniently carried out by adding ammonium hydroxide to a solution of the *N*-oxide of Formula XXVII in a suitable solvent such as dichloromethane or chloroform and then adding *p*-toluenesulfonyl chloride. The reaction can be carried out at ambient temperature. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Steps (9) and (10) can also be carried out as a one-pot procedure by first adding 3-chloroperoxybenzoic acid to a 1*H*-imidazo[4,5-*c*]quinoline of Formula XIII in a solvent such as dichloromethane or chloroform. After the reaction is stirred for a period long enough to complete the oxidation, ammonium hydroxide and *p*-toluenesulfonyl chloride are sequentially added. The reaction can be carried out at ambient temperature, and the product of Formula II or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme I



Compounds of the invention can be prepared according to Reaction Scheme II, wherein R_a, R_1, R_1', R_2, X', and n are as defined above.

In step (1) of Reaction Scheme II, a 3-nitroquinolin-4-amine of Formula XXI is reduced to provide a quinoline-3,4-diamine of Formula XXVIII. The reduction of the nitro group can be conveniently carried out as described in step (3) of Reaction Scheme I. The product can be isolated by conventional methods.

In step (2) of Reaction Scheme II, a quinoline-3,4-diamine of Formula XXVIII is reacted with a carboxylic acid or an equivalent thereof to provide a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXIX. The reaction can be conveniently carried out as described in step (4) of Reaction Scheme I; the product can be isolated by conventional methods.

In step (3) of Reaction Scheme II, the hydroxyl group of a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXIX is brominated using conventional methods to provide a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXX. The bromination is conveniently carried out by adding thionyl bromide to a solution of the 1*H*-imidazo[4,5-*c*]quinoline of Formula XIXX in a suitable solvent such as dichloromethane. The reaction can be carried out at ambient temperature, and the product can be isolated using conventional methods.

In step (4) of Reaction Scheme II, the bromo group of a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXX is displaced with sodium hydrosulfide hydrate to provide a thiol-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula XXVI. The reaction is conveniently carried out by adding sodium hydrosulfide hydrate to a solution of a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXX in a suitable solvent such as ethanol. The reaction can be carried out at ambient temperature or at an elevated temperature, such as 45 °C. The product can be isolated using conventional methods.

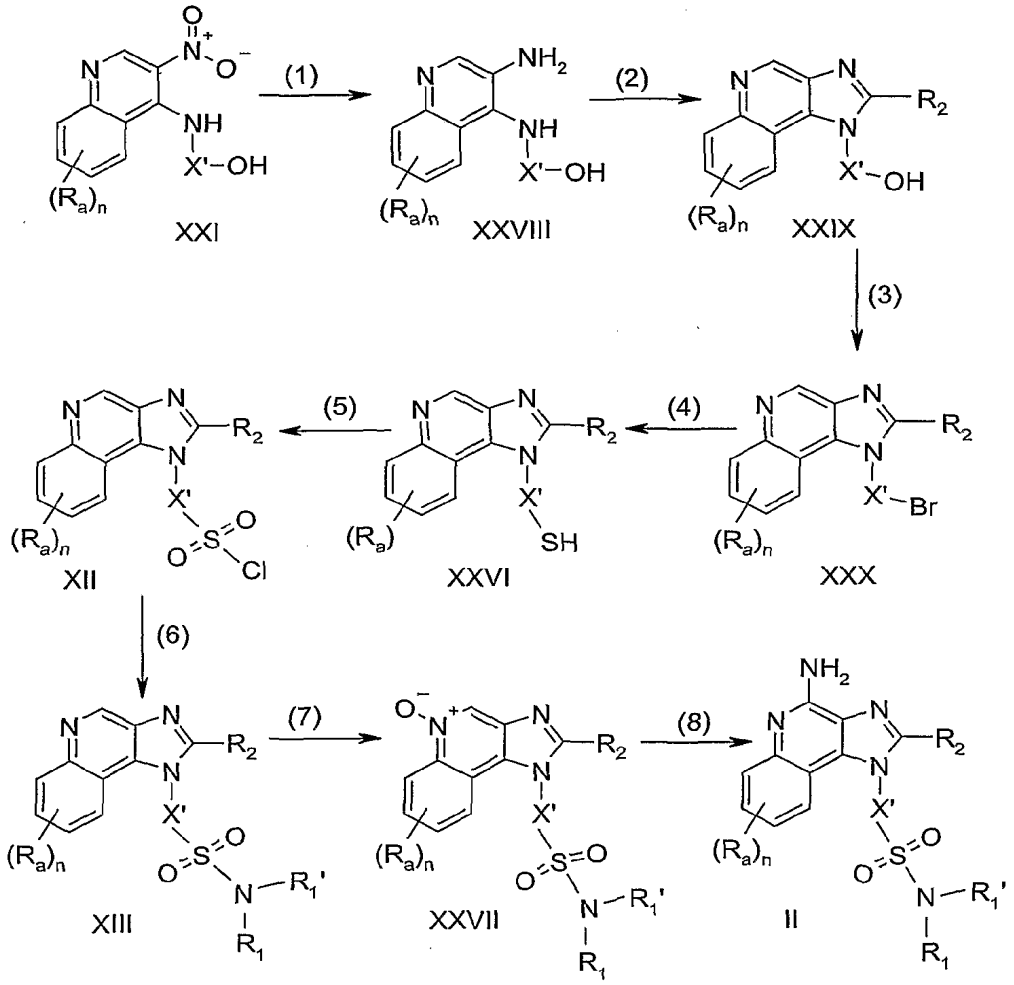
In step (5) of Reaction Scheme II, the thiol group of a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXVI is oxidized to a sulfonyl chloride of Formula XII. The reaction can be carried out as described in step (7) of Reaction Scheme I. The product can be isolated using conventional methods.

In step (6) of Reaction Scheme II, the sulfonyl chloride of Formula XII is treated with an amine or an amine salt to provide a sulfonamide of Formula XIII. The reaction can be carried out as described in step (8) of Reaction Scheme I. The product can be isolated using conventional methods.

In step (7) of Reaction Scheme II, a 1*H*-imidazo[4,5-*c*]quinoline of Formula XIII is oxidized to provide a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula XXVII using a conventional oxidizing agent capable of forming *N*-oxides. The reaction can be carried out as described in step (9) of Reaction Scheme I. The product can be isolated using conventional methods.

In step (8) of Reaction Scheme II, a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula XXVII is aminated to provide a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula II. The reaction can be carried out as described in step (10) of Reaction Scheme I. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme II



Compounds of the invention can be prepared according to Reaction Scheme III, wherein R_a, R_1, R_1', R_2, X', and n are as defined above.

In step (1) of Reaction Scheme III, the bromo group of a phthalimide of Formula XXXI is displaced with thiourea to provide a phthalimide hydrobromide of Formula XXXII. The reaction is conveniently carried out by combining a phthalimide of Formula XXXI and thiourea in a suitable solvent such as ethanol. The reaction can be carried out at an elevated temperature, such as the reflux temperature, and the product can be isolated using conventional methods. Some phthalimides of Formula XXXI, such as *N*-(3-bromopropyl)phthalimide, are commercially available; others can be prepared using known synthetic methods.

In step (2) of Reaction Scheme III, a thiourea-substituted phthalimide hydrobromide of Formula XXXII is converted to a thiourea-substituted phthalimide acetate of Formula XXXIII. The reaction is carried out by adding an aqueous solution of sodium acetate to an aqueous solution of the phthalimide hydrobromide of Formula XXXII. The reaction can be carried out at an elevated temperature, such as 100 °C, and the product can be isolated using conventional methods.

In step (3) of Reaction Scheme III, the thiourea group of a thiourea-substituted phthalimide of Formula XXXIII is converted to a sulfonyl chloride using the conditions described in step (7) of Reaction Scheme I.

In step (4) of Reaction Scheme III, a sulfonyl chloride-substituted phthalimide of Formula XXXIV is treated with an amine to provide a sulfonamido-substituted phthalimide of Formula XXXV. The reaction is conveniently carried out by adding an amine of Formula $NH(R_1)(R_1')$ to a sulfonyl chloride-substituted phthalimide of Formula XXXIV in a suitable solvent such as tetrahydrofuran. The reaction can be carried out at ambient temperature, and the product can be isolated using conventional methods.

In step (5) of Reaction Scheme III, a sulfonamido-substituted phthalimide of Formula XXXV is hydrolyzed to provide a sulfonamido-substituted amine of Formula XXXVI. The reaction is carried out by adding hydrazine hydrate to a suspension of a phthalimide of Formula XXXV in a suitable solvent such as ethanol. The reaction can be carried out at an elevated temperature, such as reflux temperature, and the product can be isolated using conventional methods.

In step (6) of Reaction Scheme III, sulfonamido-substituted amine of Formula XXXVI is reacted with a 4-chloro-3-nitroquinoline of Formula XX to provide a 3-nitroquinolin-4-amine of Formula XXXVII. The reaction is conveniently carried out by combining the amine of Formula XXXVI with a quinoline of Formula XX in the presence of a base such as triethylamine in a suitable solvent such as *N,N*-dimethylformamide. The reaction can be carried out at ambient temperature, and the product can be isolated using conventional methods.

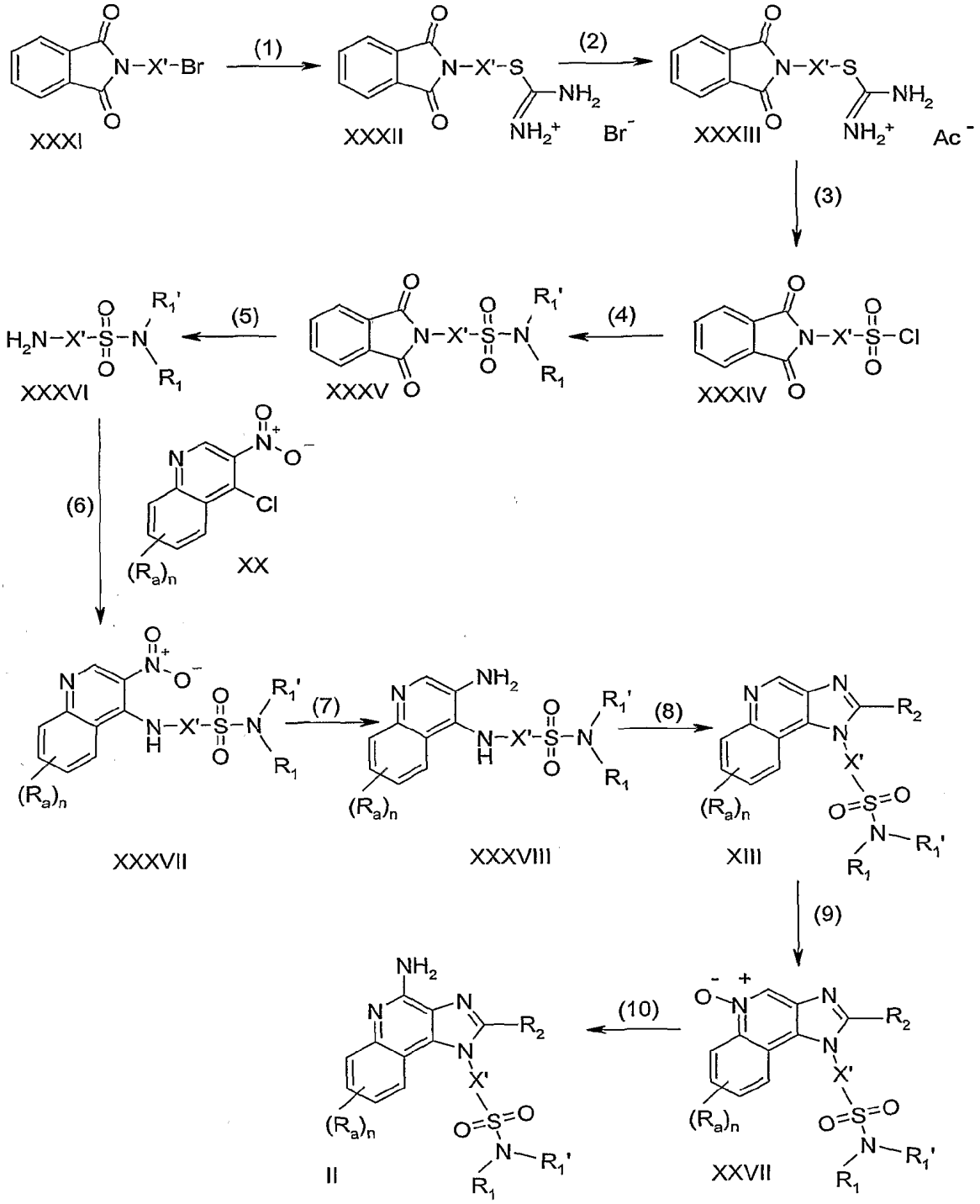
In step (7) of Reaction Scheme III, a 3-nitroquinolin-4-amine of Formula XXXVII is reduced to provide a quinoline-3,4-diamine of Formula XXXVIII. The reduction of the nitro group is carried out by hydrogenation in the presence of a heterogeneous hydrogenation catalyst, such as palladium on carbon or platinum on carbon. The reaction can be conveniently carried out on a Parr apparatus in a suitable solvent such as ethanol. The product can be isolated by conventional methods.

In step (8) of Reaction Scheme III, a quinoline-3,4-diamine of Formula XXXVIII is reacted with a carboxylic acid or an equivalent thereof to provide a 1*H*-imidazo[4,5-*c*]quinoline of Formula XIII. The reaction can be conveniently carried out as described in step (4) of Reaction Scheme I; the product can be isolated by conventional methods.

In step (9) of Reaction Scheme III, a 1*H*-imidazo[4,5-*c*]quinoline of Formula XIII is oxidized to provide a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula XXVII using a conventional oxidizing agent capable of forming *N*-oxides. The reaction can be carried out as described in step (9) of Reaction Scheme I. The product can be isolated using conventional methods.

In step (10) of Reaction Scheme III, a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula XXVII is aminated to provide a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula II. The reaction can be carried out as described in step (10) of Reaction Scheme I. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

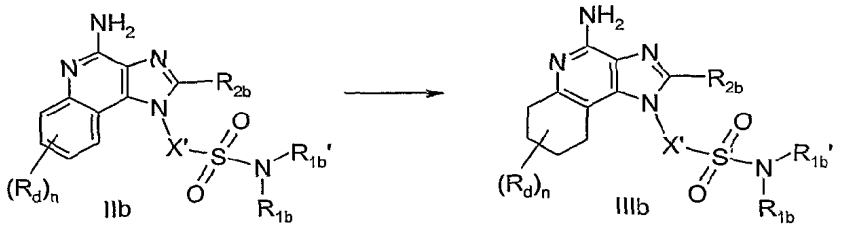
Reaction Scheme III



Compounds of the invention can also be prepared according to Reaction Scheme IV, wherein R_d is alkyl, alkoxy, or $-N(R_9)_2$ and R_{2b}, R_{1b}, and R_{1b}' are subsets of R_2, R_1, and R_1' as defined above that do not include those substituents that one skilled in the art would recognize as being susceptible to reduction under the acidic hydrogenation conditions of the reaction. These susceptible groups include, for example, alkenyl, alkynyl, and aryl groups and groups bearing nitro substituents.

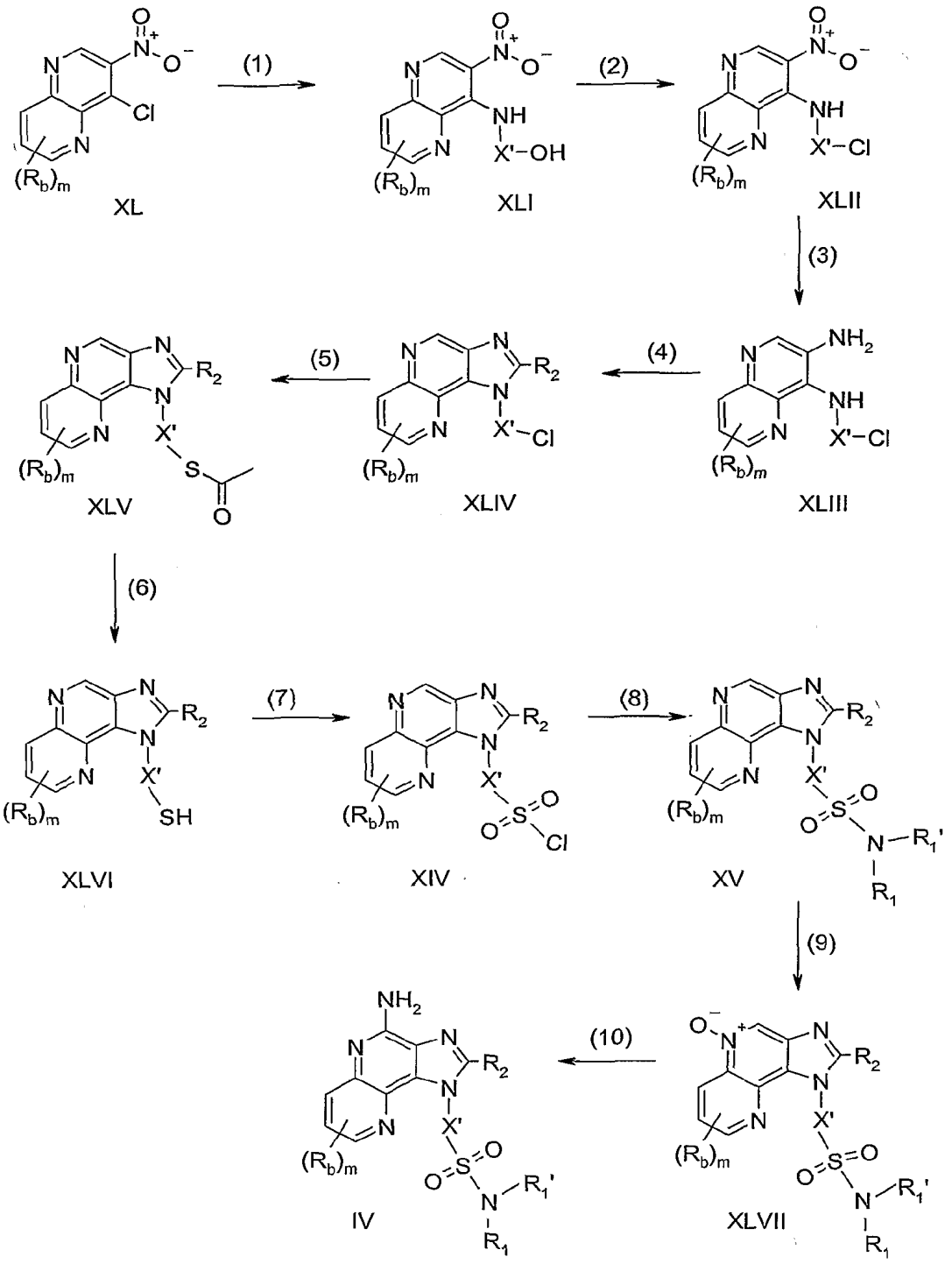
As shown in Reaction Scheme IV, an 1*H*-imidazo[4,5-*c*]quinoline of Formula IIb can be reduced to a 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula IIIb. The reaction is conveniently carried out under heterogeneous hydrogenation conditions by adding platinum (IV) oxide to a solution of the compound of Formula IIb in trifluoroacetic acid and placing the reaction under hydrogen pressure. The reaction can be carried out on a Parr apparatus at ambient temperature. The product or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

Reaction Scheme IV



Compounds of the invention can be prepared according to Reaction Scheme V, wherein R_b, R_1, R_1', R_2, X', and m are as defined above. Reaction Scheme V begins with a 4-chloro-3-nitro[1,5]naphthyridine of Formula XL. Compounds of Formula XL and their preparation are known; see, for example, U.S. Patents Nos. 6,194,425 (Gerster) and 6,518,280 (Gerster). Steps (1) through (10) of Reaction Scheme V can be carried out as described for the corresponding steps (1) through (10) of Reaction Scheme I to provide a 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine of Formula IV. The product or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

Reaction Scheme V



For some embodiments, pyridines of the invention are prepared according to Reaction Scheme VI, where R_1, R_1', R_2, $R_{A'}$, $R_{B'}$, and X' are as defined above and Ph is

phenyl. In step (1) of Reaction Scheme VI, the chloro group of a 7*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridine of Formula XLVIII is displaced with potassium thioacetate to provide a 7*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridine of Formula XLIX. The reaction can be carried out as described in step (5) of Reaction Scheme I; the product can be isolated by conventional methods. Compounds of Formula XLVIII and their preparation are known. See, for example, Dellaria et al, U.S. Publication No. US 2004/0010007 and International Publication No. WO 03/103584.

In step (2) of Reaction Scheme VI, the thioacetate group of a 7*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridine of Formula XLIX is hydrolyzed under basic conditions to provide a thiol-substituted 7*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridine of Formula L. The reaction can be carried out as described in step (6) of Reaction Scheme I; the product can be isolated by conventional methods.

In step (3) of Reaction Scheme VI, the thiol group of a 7*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridine of Formula L is oxidized to a sulfonyl chloride of Formula XVI according to the method described in step (7) of Reaction Scheme I. The product can be isolated by conventional methods.

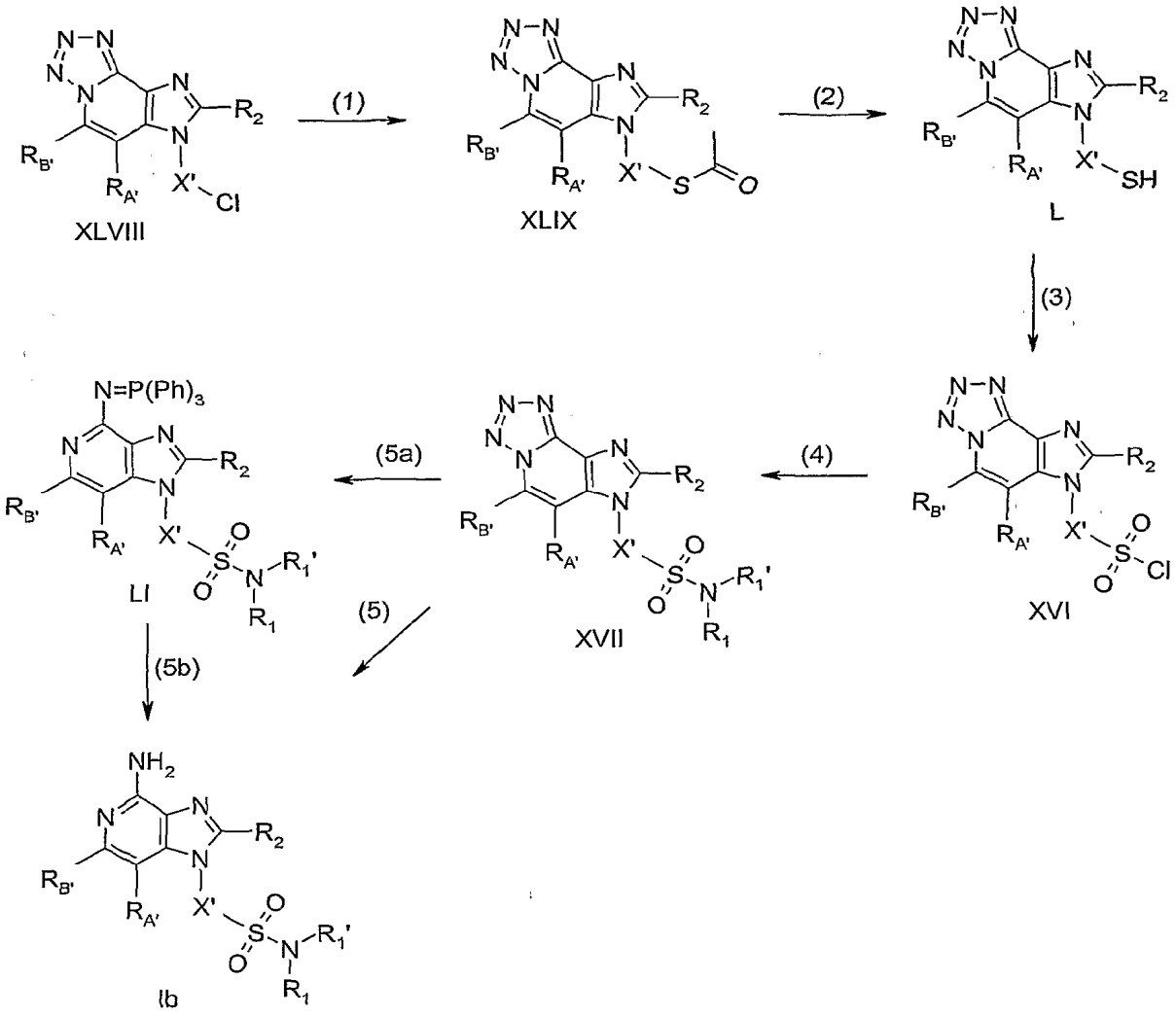
In step (4) of Reaction Scheme VI, a sulfonyl chloride of Formula XVI is treated with an amine or an amine salt to provide a sulfonamide of Formula XVII. The reaction can be carried out according to the methods described in step (8) of Reaction Scheme I, and the 7*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridine of Formula XVII can be isolated by conventional methods.

In step (5) of Reaction Scheme VI, the tetrazolo ring is reductively removed from a 7*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridine of the Formula XVII to provide a 1*H*-imidazo[4,5-*c*]pyridin-4-amine of the Formula Ib or a pharmaceutically acceptable salt thereof. The reaction can be carried out by reacting the 7*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridine of Formula XVII with hydrogen in the presence of a catalyst and an acid. The hydrogenation can be conveniently run at ambient temperature on a Parr apparatus with a suitable catalyst, such as platinum (IV) oxide, and a suitable acid, such as trifluoroacetic acid. The product or pharmaceutically acceptable salt thereof can be isolated from the reaction mixture using conventional methods.

Alternatively, the tetrazolo ring can be removed from a 7*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridine of Formula XVII as shown in step (5a) by reaction with

triphenylphosphine to form an *N*-triphenylphosphinyl intermediate of Formula LI. The reaction with triphenylphosphine can be run in a suitable solvent such as toluene or 1,2-dichlorobenzene under an atmosphere of nitrogen with heating, for example at the reflux temperature. In step (5b) of Reaction Scheme VI an *N*-triphenylphosphinyl intermediate of Formula LI is hydrolyzed to provide a 1*H*-imidazo[4,5-*c*]pyridin-4-amine of Formula Ib. The hydrolysis can be carried out by general methods well known to those skilled in the art, for example, by heating in a lower alkanol in the presence of an acid. The product can be isolated from the reaction mixture using conventional methods as the compound of Formula Ib or as a pharmaceutically acceptable salt thereof.

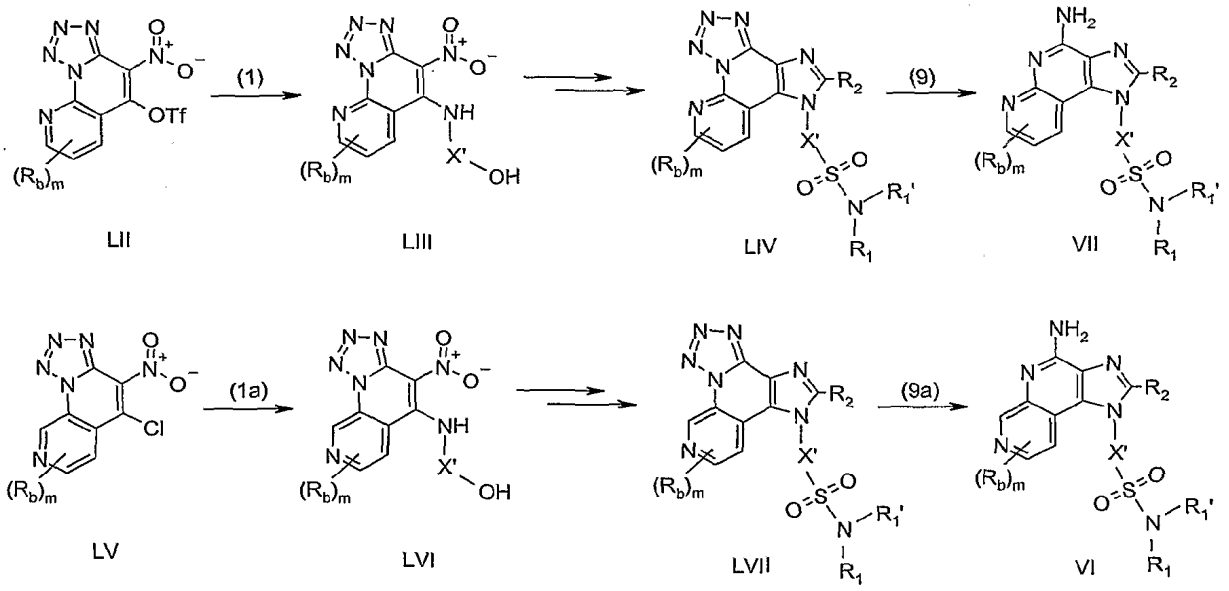
Reaction Scheme VI



For some embodiments, naphthyridines of the invention are prepared from tetrazolo compounds of Formulas LII and LV according to Reaction Scheme VII, wherein R_1, R_1', R_2, R_b, X' and m are as defined above and -OTf is a trifluoromethanesulfonate group. Compounds of Formula LII and LV and synthetic routes to these compounds are known; see, for example, U.S. Patent Nos. 6,194,425 (Gerster) and 6,518,280 (Gerster).

In steps (1) and (1a) of Reaction Scheme VII, a tetrazolonaphthyridine of Formula LII or LV is reacted with an amino alcohol of the Formula HO-X'-NH_2 to form a compound of Formula LIII or LVI. The reaction can be carried out as described in step (1) of Reaction Scheme I. A hydroxy-substituted tetrazolonaphthyridine of Formula LIII or LVI is converted to a compound of Formula LIV or LVII according to the methods of steps (2) through (8) of Reaction Scheme I. The tetrazolo group of a compound of Formula LIV or LVII can then be removed to provide a *1H-imidazo[4,5-c]naphthyridin-4-amine* of Formula VII or VI. The removal of the tetrazolo group can be carried out as described in step (5) or steps (5a) and (5b) of Reaction Scheme VI or by methods described in U.S. Patent Nos. 6,194,425 (Gerster) and 6,518,280 (Gerster). The product or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

Reaction Scheme VII



Compounds of the invention can be prepared according to Reaction Scheme VIII, wherein R_a, R_1, R_1', R_2, X', and n are as defined above.

In step (1) of Reaction Scheme VIII, a chloro-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula XXIV is oxidized and then aminated to provide a chloro-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula LVIII. The reactions can be carried out as described in steps (9) and (10) of Reaction Scheme I. The product can be isolated using conventional methods.

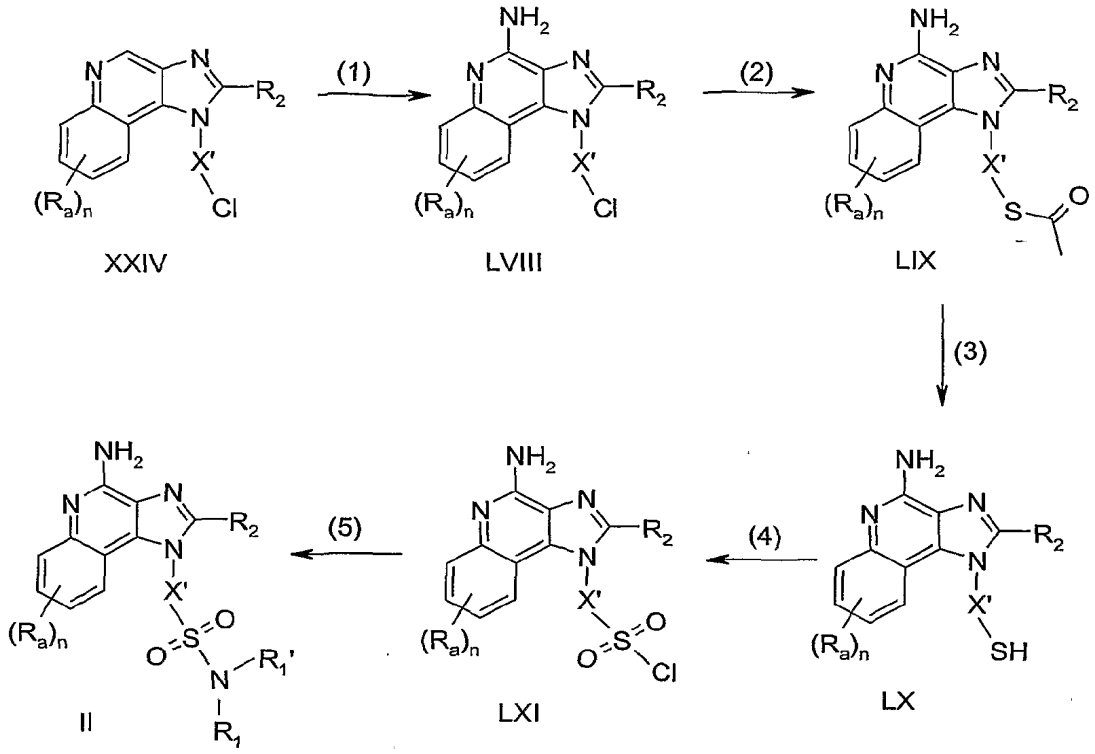
In step (2) of Reaction Scheme VIII, the chloro group of a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula LVIII is displaced with potassium thioacetate to provide a thioacetate-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula LIX. The reaction can be carried out as described in step (5) of Reaction Scheme I. The product can be isolated using conventional methods.

In step (3) of Reaction Scheme VIII, a thioacetate-substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula LIX is hydrolyzed provide a thiol-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula LX. The reaction can be carried out as described in step (6) of Reaction Scheme I. The product can be isolated using conventional methods.

In step (4) of Reaction Scheme VIII, a thiol-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula LX is oxidized to a sulfonyl chloride of Formula LXI. The reaction can be carried out as described in step (7) of Reaction Scheme I. The product can be isolated using conventional methods.

In step (5) of Reaction Scheme VIII, a sulfonyl chloride of Formula LXI is treated with an amine or an amine salt to provide a sulfonamide of Formula II. The reaction can be carried out as described in step (8) of Reaction Scheme I. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme VIII



Compounds of the invention can be prepared according to Reaction Scheme IX, wherein R_a, R_1, R_1', R_2, X', and n are as defined above and Ts is (4-methylphenyl)sulfonyl.

In step (1) of Reaction Scheme IX, a hydroxy substituted 3-nitroquinolin-4-amine of Formula XXI is reacted with tosyl chloride to provide a 4-amino-3-nitroquinolinyl *p*-tolunesulfonate of Formula LXII. The reaction is conveniently carried out by combining tosyl chloride with a quinoline of Formula XXI in the presence of 4-dimethylaminopyridine in a suitable solvent such as pyridine. The reaction can be carried out at ambient temperature and the product can be isolated using conventional methods.

In step (2) of Reaction Scheme IX, a 4-amino-3-nitroquinolinyl *p*-toluenesulfonate of Formula LXII is reduced to provide a 3,4-diaminoquinolinyl *p*-toluenesulfonate of Formula LXIII. The reduction can be carried out as described in step (3) of Reaction Scheme I and the product can be isolated using conventional methods.

In step (3) of Reaction Scheme IX, a 3,4-diaminoquinolinyl *p*-toluenesulfonate of Formula LXIII is reacted with a carboxylic acid or an equivalent thereof to provide a 1*H*-imidazo[4,5-*c*]quinoline of Formula LXIV. The reaction can be carried out as described in step (3) of Reaction Scheme I and the product can be isolated using conventional methods.

In step (4) of Reaction Scheme IX, the *p*-toluenesulfonate group of a 1*H*-imidazo[4,5-*c*]quinoline of Formula LXIV is displaced with potassium thiocyanate to provide a thiocyanate substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula LXV. The reaction can be carried out by adding potassium thiocyanate to a solution of a 1*H*-imidazo[4,5-*c*]quinoline of Formula LXIV in a suitable solvent such as *n*-propanol. The reaction can be carried out at an elevated temperature, such as 180 – 190 °C, using a microwave synthesizer and the product can be isolated using conventional methods.

In step (5) of Reaction Scheme IX, the thiocyanate group of a 1*H*-imidazo[4,5-*c*]quinoline of Formula LXV is cleaved to provide a thiol substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula XXVI. The reaction can be carried out by adding sodium borohydride to a solution of a 1*H*-imidazo[4,5-*c*]quinoline of Formula LXV in a suitable solvent such as ethanol. The reaction can be carried out at a sub-ambient temperature such as 0 °C and the product can be isolated using conventional methods.

In step (6) of Reaction Scheme IX, the thiol group of a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXVI is oxidized to provide a sulfonyl chloride of Formula XXII. The reaction is carried out by treating a solution of a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXVI in a suitable solvent such as dichloromethane with chlorine, prepared *in situ* from benzyltrimethylammonium chloride and trichloroisocyanuric acid. The reaction can be carried out at a sub-ambient temperature such as 0 °C and the product can be isolated using conventional methods.

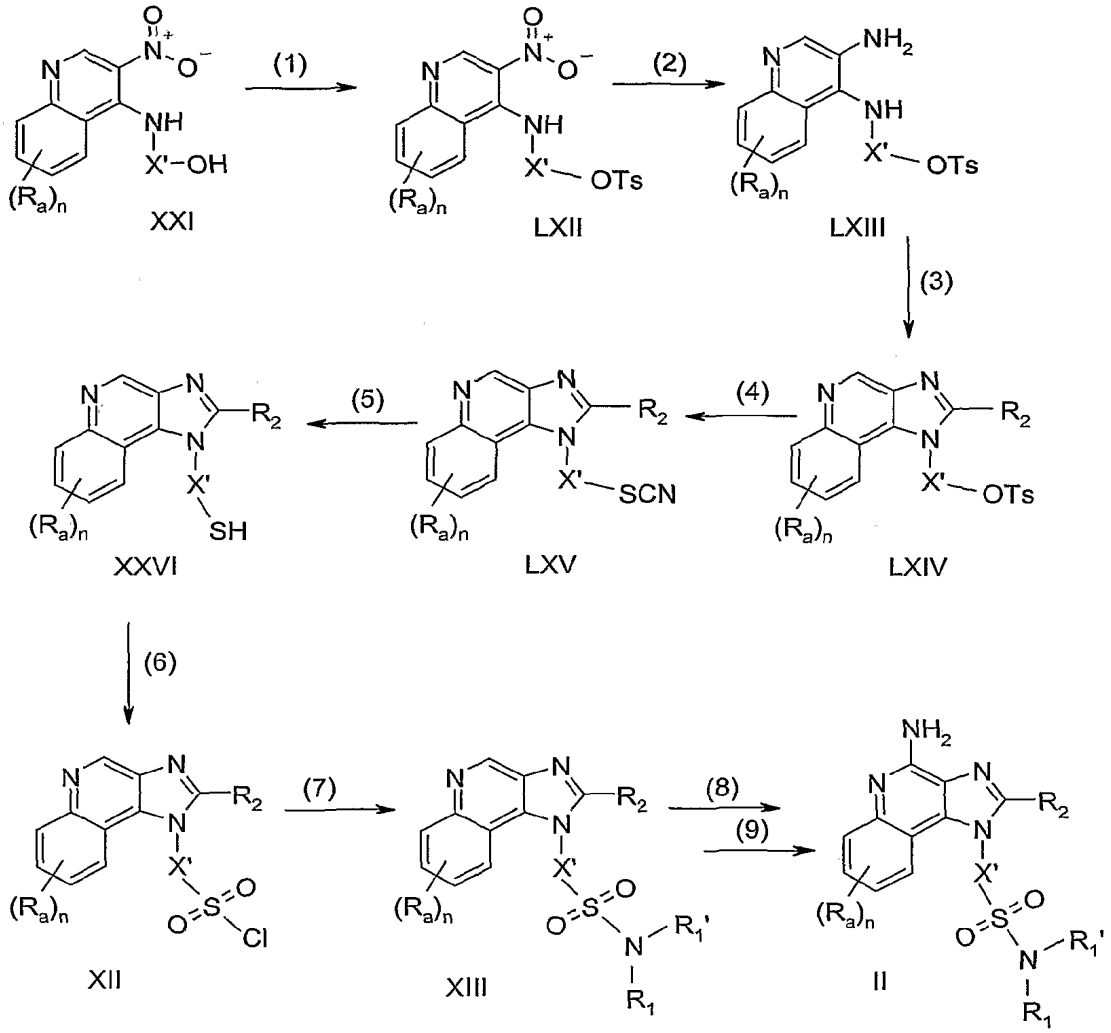
In step (7) of Reaction Scheme IX, a sulfonyl chloride of Formula XXII is reacted with an amine or amine salt to provide a sulfonamide substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula XIII. The reaction can be carried out at described in step (8) of Reaction Scheme I and the product can be isolated using conventional methods.

Steps (6) and (7) are preferably carried out as a one pot procedure by first treating a chilled solution of a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXVI in a suitable solvent such as dichloromethane with chlorine, prepared *in situ* from benzyltrimethylammonium chloride and trichloroisocyanuric acid. After the reaction is stirred for a period long

enough to complete the oxidation, the amine is added and the reaction mixture is allowed to warm to ambient temperature.

In steps (8) and (9) of Reaction Scheme IX, a 1*H*-imidazo[4,5-*c*]quinoline of Formula XIII is oxidized and then aminated to provide a 1*H*-imidazo[4,5-*c*]quinoline-4-amine of Formula II. The reactions can be carried out as described in steps (9) and (10) respectively of Reaction Scheme I. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme IX



Compounds of the invention can also be prepared using variations of the synthetic routes shown in Reaction Schemes I through IX. For example, tetrahydronaphthyridines can be prepared using the reduction method described in Reaction Scheme IV for the preparation of tetrahydroquinolines. Compounds of the invention can also be prepared using the synthetic routes described in the EXAMPLES below.

Pharmaceutical Compositions and Biological Activity

Pharmaceutical compositions of the invention contain a therapeutically effective amount of a compound or salt of the invention as described above in combination with a pharmaceutically acceptable carrier.

The terms "a therapeutically effective amount" and "effective amount" mean an amount of the compound or salt sufficient to induce a therapeutic or prophylactic effect, such as cytokine induction, immunomodulation, antitumor activity, and/or antiviral activity. Although the exact amount of active compound or salt used in a pharmaceutical composition of the invention will vary according to factors known to those of skill in the art, such as the physical and chemical nature of the compound or salt, the nature of the carrier, and the intended dosing regimen, it is anticipated that the compositions of the invention will contain sufficient active ingredient to provide a dose of about 100 nanograms per kilogram (ng/kg) to about 50 milligrams per kilogram (mg/kg), preferably about 10 micrograms per kilogram (μg/kg) to about 5 mg/kg, of the compound or salt to the subject. A variety of dosage forms may be used, such as tablets, lozenges, capsules, parenteral formulations, syrups, creams, ointments, aerosol formulations, transdermal patches, transmucosal patches and the like.

The compounds or salts of the invention can be administered as the single therapeutic agent in the treatment regimen, or the compounds or salts of the invention may be administered in combination with one another or with other active agents, including additional immune response modifiers, antivirals, antibiotics, antibodies, proteins, peptides, oligonucleotides, etc.

Compounds or salts of the invention have been shown to induce the production of certain cytokines in experiments performed according to the test set forth below. These results indicate that the compounds or salts are useful as immune response modifiers that

can modulate the immune response in a number of different ways, rendering them useful in the treatment of a variety of disorders.

Cytokines whose production may be induced by the administration of compounds or salts of the invention generally include interferon-α (IFN-α) and/or tumor necrosis factor-α (TNF-α) as well as certain interleukins (IL). Cytokines whose biosynthesis may be induced by compounds or salts of the invention include IFN-α, TNF-α, IL-1, IL-6, IL-10 and IL-12, and a variety of other cytokines. Among other effects, these and other cytokines can inhibit virus production and tumor cell growth, making the compounds or salts useful in the treatment of viral diseases and neoplastic diseases. Accordingly, the invention provides a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt or composition of the invention to the animal. The animal to which the compound or salt or composition is administered for induction of cytokine biosynthesis may have a disease as described *infra*, for example a viral disease or a neoplastic disease, and administration of the compound or salt may provide therapeutic treatment. Alternatively, the compound or salt may be administered to the animal prior to the animal acquiring the disease so that administration of the compound or salt may provide a prophylactic treatment.

In addition to the ability to induce the production of cytokines, compounds or salts of the invention can affect other aspects of the innate immune response. For example, natural killer cell activity may be stimulated, an effect that may be due to cytokine induction. The compounds or salts may also activate macrophages, which in turn stimulate secretion of nitric oxide and the production of additional cytokines. Further, the compounds or salts may cause proliferation and differentiation of B-lymphocytes.

Compounds or salts of the invention can also have an effect on the acquired immune response. For example, the production of the T helper type 1 (T_H1) cytokine IFN-γ may be induced indirectly and the production of the T helper type 2 (T_H2) cytokines IL-4, IL-5 and IL-13 may be inhibited upon administration of the compounds or salts.

Whether for prophylaxis or therapeutic treatment of a disease, and whether for effecting innate or acquired immunity, the compound or salt or composition may be administered alone or in combination with one or more active components as in, for example, a vaccine adjuvant. When administered with other components, the compound or salt and other component or components may be administered separately; together but

independently such as in a solution; or together and associated with one another such as (a) covalently linked or (b) non-covalently associated, e.g., in a colloidal suspension.

Conditions for which compounds or salts identified herein may be used as treatments include, but are not limited to:

(a) viral diseases such as, for example, diseases resulting from infection by an adenovirus, a herpesvirus (e.g., HSV-I, HSV-II, CMV, or VZV), a poxvirus (e.g., an orthopoxvirus such as variola or vaccinia, or molluscum contagiosum), a picornavirus (e.g., rhinovirus or enterovirus), an orthomyxovirus (e.g., influenzavirus), a paramyxovirus (e.g., parainfluenzavirus, mumps virus, measles virus, and respiratory syncytial virus (RSV)), a coronavirus (e.g., SARS), a papovavirus (e.g., papillomaviruses, such as those that cause genital warts, common warts, or plantar warts), a hepadnavirus (e.g., hepatitis B virus), a flavivirus (e.g., hepatitis C virus or Dengue virus), or a retrovirus (e.g., a lentivirus such as HIV);

(b) bacterial diseases such as, for example, diseases resulting from infection by bacteria of, for example, the genus Escherichia, Enterobacter, Salmonella, Staphylococcus, Shigella, Listeria, Aerobacter, Helicobacter, Klebsiella, Proteus, Pseudomonas, Streptococcus, Chlamydia, Mycoplasma, Pneumococcus, Neisseria, Clostridium, Bacillus, Corynebacterium, Mycobacterium, Campylobacter, Vibrio, Serratia, Providencia, Chromobacterium, Brucella, Yersinia, Haemophilus, or Bordetella;

(c) other infectious diseases, such chlamydia, fungal diseases including but not limited to candidiasis, aspergillosis, histoplasmosis, cryptococcal meningitis, or parasitic diseases including but not limited to malaria, pneumocystis carnii pneumonia, leishmaniasis, cryptosporidiosis, toxoplasmosis, and trypanosome infection;

(d) neoplastic diseases, such as intraepithelial neoplasias, cervical dysplasia, actinic keratosis, basal cell carcinoma, squamous cell carcinoma, renal cell carcinoma, Kaposi's sarcoma, melanoma, leukemias including but not limited to myelogeous leukemia, chronic lymphocytic leukemia, multiple myeloma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, B-cell lymphoma, and hairy cell leukemia, and other cancers;

(e) T_H2-mediated, atopic diseases, such as atopic dermatitis or eczema, eosinophilia, asthma, allergy, allergic rhinitis, and Ommen's syndrome;

(f) certain autoimmune diseases such as systemic lupus erythematosus, essential thrombocythaemia, multiple sclerosis, discoid lupus, alopecia areata; and

(g) diseases associated with wound repair such as, for example, inhibition of keloid formation and other types of scarring (e.g., enhancing wound healing, including chronic wounds).

Additionally, compounds or salts of the present invention may be useful as a vaccine adjuvant for use in conjunction with any material that raises either humoral and/or cell mediated immune response, such as, for example, live viral, bacterial, or parasitic immunogens; inactivated viral, tumor-derived, protozoal, organism-derived, fungal, or bacterial immunogens, toxoids, toxins; self-antigens; polysaccharides; proteins; glycoproteins; peptides; cellular vaccines; DNA vaccines; autologous vaccines; recombinant proteins; and the like, for use in connection with, for example, BCG, cholera, plague, typhoid, hepatitis A, hepatitis B, hepatitis C, influenza A, influenza B, parainfluenza, polio, rabies, measles, mumps, rubella, yellow fever, tetanus, diphtheria, hemophilus influenza b, tuberculosis, meningococcal and pneumococcal vaccines, adenovirus, HIV, chicken pox, cytomegalovirus, dengue, feline leukemia, fowl plague, HSV-1 and HSV-2, hog cholera, Japanese encephalitis, respiratory syncytial virus, rotavirus, papilloma virus, yellow fever, and Alzheimer's Disease.

Compounds or salts of the present invention may be particularly helpful in individuals having compromised immune function. For example, compounds or salts may be used for treating the opportunistic infections and tumors that occur after suppression of cell mediated immunity in, for example, transplant patients, cancer patients and HIV patients.

Thus, one or more of the above diseases or types of diseases, for example, a viral disease or a neoplastic disease may be treated in an animal in need thereof (having the disease) by administering a therapeutically effective amount of a compound or salt of the invention to the animal.

An amount of a compound or salt effective to induce cytokine biosynthesis is an amount sufficient to cause one or more cell types, such as monocytes, macrophages, dendritic cells and B-cells to produce an amount of one or more cytokines such as, for example, IFN-α, TNF-α, IL-1, IL-6, IL-10 and IL-12 that is increased (induced) over a background level of such cytokines. The precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. The invention also provides a method of

treating a viral infection in an animal and a method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound or salt or composition of the invention to the animal. An amount effective to treat or inhibit a viral infection is an amount that will cause a reduction in one or more of the manifestations of viral infection, such as viral lesions, viral load, rate of virus production, and mortality as compared to untreated control animals. The precise amount that is effective for such treatment will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. An amount of a compound or salt effective to treat a neoplastic condition is an amount that will cause a reduction in tumor size or in the number of tumor foci. Again, the precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg.

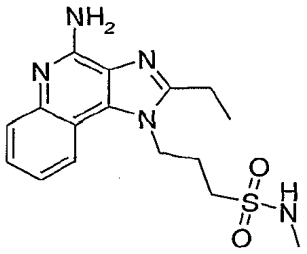
Objects and advantages of this invention are further illustrated by the following examples, but the particular materials and amounts thereof recited in these examples, as well as other conditions and details, should not be construed to unduly limit this invention.

EXAMPLES

In the examples below high performance flash chromatography (HPFC) was carried out using either a HORIZON HPFC system (an automated high-performance flash purification product available from Biotage, Inc, Charlottesville, Virginia, USA) or an INTELLIFLASH Flash Chromatography System (an automated flash purification system available from AnaLogix, Inc, Burlington, Wisconsin, USA). The eluent used for each purification is given in the example. In some chromatographic separations, the solvent mixture 80/18/2 v/v/v chloroform/methanol/concentrated ammonium hydroxide (CMA) was used as the polar component of the eluent. In these separations, CMA was mixed with chloroform in the indicated ratio.

Example 1

N-Methyl 3-(4-amino-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propane-1-sulfonamide



Part A

A suspension of *N*-(3-bromopropyl)phthalimide (10.0 g, 37.3 mmol, 1.0 eq,) and thiourea (2.84 g, 1.0 eq.) was heated at reflux for 8 hours and then allowed to cool to ambient temperature overnight. The resulting precipitate was isolated by filtration and rinsed with ethanol (3 x 7 mL) to provide 12.16 g of 2-[3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)propyl]isothiourea hydrobromide as a white solid, m.p. 170-172°C.

Part B

Saturated hot aqueous sodium acetate (~7 mL, ~ 4eq.) was added to a stirred solution of 2-[3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)propyl]isothiourea hydrobromide (12.16 g, 35.32 mmol) in hot (100 °C) water (90 mL). The reaction mixture was allowed to cool to ambient temperature overnight. The resulting precipitate was isolated by

filtration, washed with cold water (2 x 15 mL), and dried at 35°C under vacuum to provide 8.77 g of 2-[4-(1,3-dioxo-1,3-dihydroisoindol-2-yl)propyl]isothiourea acetic acid salt as a white solid, m.p. 152-153 °C.

Part C

A solution of sodium chlorate (983 mg, 1.25 eq.) in water (2 mL) was added dropwise with stirring over a period of 5 minutes to a chilled (0 °C) suspension of 2-[3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)propyl]isothiourea acetic acid salt (2.39 g, 7.39 mmol, 1.0 eq.) in concentrated hydrochloric acid (10 mL). The reaction mixture was stirred for 30 minutes. A pale yellow solid was isolated by filtration, washed with ice cold water (2 x 10 mL), and dried under vacuum to provide 1.81 g of product. This material was stirred with chloroform (25 mL) and then filtered to remove an insoluble white solid. The filtrate was concentrated under reduced pressure to provide 1.33 g of 3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)propane-1-sulfonyl chloride as a crystalline solid, m.p. 76-79 °C.

Part D

Methylamine (4.45 mL of 2.0 M in tetrahydrofuran, 2.0 eq.) was added dropwise with stirring to a solution of 3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)propane-1-sulfonyl chloride (1.28 g, 4.45 mmol. 1.0 eq.) in tetrahydrofuran (THF). The reaction mixture was stirred for 2 hours and then concentrated under reduced pressure. The residue was taken up in chloroform (110 mL) and washed with water (35 mL). The aqueous wash was back extracted with chloroform (40 mL). The combined organics were dried over magnesium sulfate and concentrated under reduced pressure to provide 1.11 g of *N*-methyl 3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)propane-1-sulfonamide as a white solid.

Part E

Hydrazine hydrate (290 μL, 1.3 eq.) was added dropwise with stirring to a suspension of *N*-methyl 3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)propane-1-sulfonamide (1.10 g, 3.90 mmol, 1.0 eq.) in ethanol (20 mL). The reaction mixture was heated to reflux. After 3.5 hours analysis by 1H NMR indicated that the reaction was about a 60:40 mixture of product and starting material. At 4.5 hours additional hydrazine hydrate (0.7 eq.) was added. After an additional 2 hours analysis by 1H NMR indicated that the

reaction was complete. The reaction was allowed to cool to ambient temperature over the weekend and then concentrated under reduced pressure. The residue was dissolved in water (10 mL). Concentrated hydrochloric acid (0.65 mL, 2.0 eq.) was added dropwise to provide a thick white precipitate. The mixture was diluted with water (10 mL), stirred for 20 minutes, and filtered; the filter cake was rinsed with water (3 x 10 mL). The filtrate was concentrated under reduced pressure to provide 0.82 g of *N*-methyl 3-aminopropane-1-sulfonamide hydrochloride as a pale yellow solid.

Part F

Triethylamine (1.14 mL, 2.1 eq.) was added to a stirred solution of *N*-methyl 3-aminopropane-1-sulfonamide hydrochloride (0.82 g, 3.90 mmol, 1.0 eq.) in *N,N*-dimethylformamide (DMF, 19.5 mL). 4-Chloro-3-nitroquinoline (813 mg, 3.90 mmol, 1.0 eq) was added to the resulting suspension in a single portion. The reaction mixture was stirred at ambient temperature for 1 hour and then concentrated under reduced pressure. The residue was partitioned between chloroform (100 mL) and water (30 mL). The aqueous layer was back extracted with chloroform (20 mL). The combined organics were dried over magnesium sulfate and then concentrated under reduced pressure to provide crude product as a yellow solid. The solid was triturated with diethyl ether (30 mL), isolated by filtration, and rinsed with diethyl ether (3 x 10 mL) to provide 0.85 g of *N*-methyl 3-[(3-nitroquinolin-4-yl)amino]propane-1-sulfonamide as a yellow solid.

Part G

A suspension of *N*-methyl 3-[(3-nitroquinolin-4-yl)amino]propane-1-sulfonamide (0.45 g, 1.39 mmol) and 5% platinum on carbon (90 mg) in ethanol (30 mL) was hydrogenated at 35 psi (2.4 x 10^5 Pa). After 3 hours analysis by thin layer chromatography (TLC) indicated that the reaction was complete. The reaction mixture was filtered to remove the catalyst and the filter cake was rinsed with ethanol (2 x 15 mL). The filtrate was concentrated under reduced pressure to provide 0.43 g of *N*-methyl 3-[(3-aminoquinolin-4-yl)amino]propane-1-sulfonamide as an orange oil.

Part H

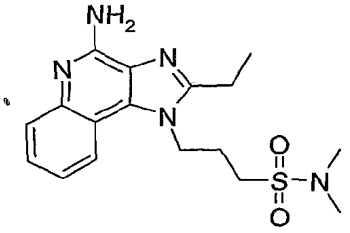
Triethyl orthopropionate (308 μL, 1.1 eq.) was added to a stirred solution of the material from Part G (1.39 mmol, 1.0 eq.) in pyridine (7 mL). Pyridine hydrochloride (16 mg, 0.1 eq.) was added and the reaction mixture was heated at 100 °C for 2 hours. Analysis by TLC indicated that the reaction was complete at 1.5 hours. The reaction mixture was cooled to ambient temperature and then concentrated under reduced pressure. The residue was partitioned between chloroform (60 mL) and water (35 mL). The aqueous layer was back extracted with chloroform (20 mL). The combined organics were dried over magnesium sulfate and then concentrated under reduced pressure to provide crude product as a brown oil. The oil was purified by column chromatography (silica gel eluting with 10/90 methanol/chloroform) to provide 336 mg of *N*-methyl 3-(2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propane-1-sulfonamide as a tan solid.

Part I

3-Chloroperoxybenzoic acid (98 mg, 1.2 eq.) was added to a suspension of *N*-methyl 3-(2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propane-1-sulfonamide (110 mg, 0.33 mmol, 1.0 eq.) in chloroform (1.7 mL). All of the suspended material gradually went into solution. After 30 minutes analysis by TLC indicated that all the starting material had been consumed. After 1 hour concentrated ammonium hydroxide (2 mL) was added followed by tosyl chloride (76 mg, 1.2 eq.). The resulting biphasic mixture was stirred vigorously for 3 hours then the organic layer was separated. The aqueous layer was extracted with chloroform (3 x 2 mL). The extracts were combined with the original organic layer, dried over magnesium sulfate and concentrated under reduced pressure to provide 0.12 g of crude product as a tan foam. The foam was recrystallized from THF (~ 3 mL), isolated by filtration, and rinsed with ice cold THF (2 x 2 mL) to provide 32 mg of *N*-methyl 3-(4-amino-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propane-1-sulfonamide as a tan powder, mp 225-228°C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.11 (d, J=7.6 Hz, 1H), 7.61 (dd, J=1.1, 8.4 Hz, 1H), 7.42 (t, J=7.2 Hz, 1H), 7.25 (dd, J=1.2, 8.1 Hz, 1H), 6.95 (q, J=4.9 Hz, 1H), 6.45 (s, 2H), 4.64 (t, J=7.7 Hz, 2H), 3.29 (m, 2H), 2.96 (q, J=7.5 Hz, 2H), 2.56 (d, J=4.9 Hz, 3H), 2.14 (m, 2H), 1.38 (t, J=7.4 Hz, 3H); MS (APCI) *m/z*: 348 (M+H). Anal. calcd. for $C_{16}H_{21}N_5O_2S$•0.08THF•0.14 H_2O: C, 55.10; H, 6.21; N, 19.69. Found: C, 55.04; H, 6.19; N, 19.37.

Example 2

N,N-Dimethyl 3-(4-amino-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propane-1-sulfonamide



Part A

Dimethylamine (4.7 mL of 2.0 M in tetrahydrofuran, 2.1 eq.) was added dropwise with stirring to a solution of 3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)propane-1-sulfonyl chloride (5.04 g, 17.5 mmol. 1.0 eq.) in tetrahydrofuran (THF). The reaction mixture was stirred for 1.5 hours and then concentrated under reduced pressure. The residue was dissolved in chloroform (120 mL), washed with water (50 mL), dried over magnesium sulfate and concentrated under reduced pressure to provide 3.80 g of crude *N,N*-dimethyl 3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)propane-1-sulfonamide as a white solid.

Part B

Hydrazine hydrate (0.95 mL, 1.3 eq.) was added dropwise with stirring to a suspension of the crude product from Part A (1.0 eq.) in ethanol (60 mL). The reaction mixture was heated at reflux for 3 hours, allowed to cool to ambient temperature, and then concentrated under reduced pressure. The residue was suspended in water (80 mL). Concentrated hydrochloric acid (1.6 mL, 1.5 eq.) was added dropwise. The resulting suspension was stirred vigorously for 45 minutes and filtered; the filter cake was rinsed with water (2 x 35 mL). The filtrate was concentrated under reduced pressure to provide a white solid. This material was combined with methanol (50 mL) and then concentrated under reduced pressure. This procedure was repeated with acetonitrile (100 mL) to provide 2.50 g of *N,N*-dimethyl 3-aminopropane-1-sulfonamide hydrochloride as a white solid.

Part C

4-Chloro-3-nitroquinoline (2.34 g, 11.2 mmol, 1.0 eq.) was added in a single portion to a stirred solution of the material from Part B (12.3 mmol, 1.10 eq.) in DMF (45 mL). Triethylamine (3.3 mL, 2.1 eq.) was added dropwise. After 1 hour analysis by TLC indicated that the reaction was complete. The reaction mixture was concentrated under reduced pressure. The residue was partitioned between chloroform (200 mL) and water (50 mL). The aqueous layer was back extracted with chloroform (75 mL). The combined organics were dried over magnesium sulfate and then concentrated under reduced pressure to provide 2.72 g of *N,N*-dimethyl 3-[(3-nitroquinolin-4-yl)amino]propane-1-sulfonamide as a red solid.

Part D

Sodium borohydride (1.20 g, 4.0 eq.) was slowly added to a stirred solution of *N,N*-dimethyl 3-[(3-nitroquinolin-4-yl)amino]propane-1-sulfonamide (2.68 g, 7.92 mmol, 1.0 eq.) and nickel (II) chloride hexahydrate (188 mg, 0.1 eq.) in 1/1 methanol/chloroform (40 mL). After 30 minutes analysis by TLC indicated that the reaction was complete. The reaction mixture was concentrated under reduced pressure. The residue was suspended in chloroform (200 mL), washed with water (2 x 60 mL), dried over magnesium sulfate, and then concentrated under reduced pressure to provide a brown oil. TLC analysis of the oil showed multiple components. The combined aqueous washes were made basic (pH 8-9) and then extracted with chloroform (2 x 75 mL). The chloroform extracts were combined, dried over magnesium sulfate, and then concentrated under reduced pressure to provide 1.46 g of *N,N*-dimethyl 3-[(3-aminoquinolin-4-yl)amino]propane-1-sulfonamide as a brown foam.

Part E

Pyridine hydrochloride (55 mg, 0.1 eq.) was added to a stirred solution of the material from Part D (4.73 mmol, 1.0 eq.) in pyridine (24 mL). Triethyl orthopropionate (1.05 mL, 1.1 eq.) was added and the reaction mixture was heated at 100 °C for 2.5 hours. Analysis by TLC indicated that the reaction was complete. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in chloroform (140 mL), washed with water (2 x 35 mL), dried over magnesium sulfate, and then concentrated

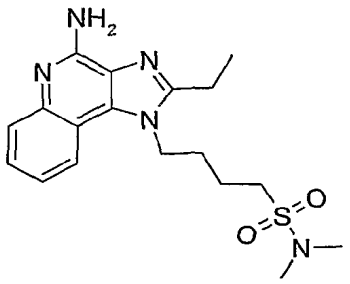
under reduced pressure to give crude product as a brown foam. This material was purified by column chromatography (silica gel eluting with 1.5/98.5 methanol/chloroform) to provide 1.08 g of *N,N*-dimethyl 3-(2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propane-1-sulfonamide as a brown foam.

Part F

3-Chloroperoxybenzoic acid (810 mg, 1.2 eq.) was added in a single portion to a solution of *N,N*-dimethyl 3-(2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propane-1-sulfonamide (0.95 g, 2.74 mmol, 1.0 eq.) in chloroform (14 mL). After 30 minutes analysis by TLC indicated that all of the starting material had been consumed. After 2 hours concentrated ammonium hydroxide (14 mL) was added followed by tosyl chloride (679 mg, 1.3 eq.). The resulting biphasic mixture was stirred vigorously for 2.5 hours then the organic layer was separated. The aqueous layer was extracted with chloroform (2 x 20 mL). All organics were combined, dried over magnesium sulfate and then concentrated under reduced pressure to provide 1.25 g of crude product as a brown foam. The foam was triturated with ethyl acetate (7 mL), combined with petroleum ether, isolated by filtration, rinsed with 1/1 ethyl acetate petroleum ether (3 x 2 mL), and dried under vacuum at 70 °C for 4 days to provide 770 mg of an off white powder. This powder was combined with chloroform (80 mL), washed with saturated aqueous sodium bicarbonate (30 mL), dried over magnesium sulfate, and then concentrated under reduced pressure. The resulting solid was recrystallized from ethanol (~ 25 mL), isolated by filtration, rinsed with ice cold ethanol (2 x 5 mL), and then dried to provide 553 mg of *N,N*-dimethyl 3-(4-amino-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propane-1-sulfonamide as an off white powder, mp 209-211°C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.11 (m, 1H), 7.61 (dd, J=1.0, 8.3 Hz, 1H), 7.42 (m, 1H), 7.25 (m, 1H), 6.45 (br s, 2H), 4.64 (t, J=8.0 Hz, 2H), 3.35 (m, 2H), 2.96 (q, J=7.4 Hz, 2H), 2.77 (s, 6H), 2.18 (m, 2H), 1.38 (t, J=7.4 Hz, 3H); MS (APCI) *m/z*: 362 $(M+H)^+$; Anal. calcd. for $C_{17}H_{23}N_5O_2S$: C, 56.49; H, 6.41; N, 19.37. Found: C, 56.56; H, 6.31; N, 19.44

Example 3

N,N-Dimethyl 4-(4-amino-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide



Part A

Triethylamine (11.8 g, 57.2 mmol, 1.1.eq.) was added to a suspension of 4-chloro-3-nitroquinoline (20 g, 47.9 mmol, 1 eq.) in dichloromethane (200 mL). A solution of 4-aminobutanol (9.6 g, 52.7 mmol, 1.1 eq.) in dichloromethane (50 mL) was slowly added. After 2 hours the reaction mixture was concentrated under reduced pressure. The residue was slurried with water for about an hour. The resulting solid was isolated by filtration and air dried to provide crude product. This material was purified by column chromatography (silica gel eluting sequentially with dichloromethane and 5% methanol in dichloromethane) to provide 24.1 g of 4-[(3-nitroquinolin-4-yl)amino]butanol.

Part B

A suspension of 4-[(3-nitroquinolin-4-yl)amino]butanol (18.2 g, 69.6 mmol) and 5 % palladium on carbon in a mixture of toluene (450 mL) and ethanol (60 mL) was hydrogenated on a Parr apparatus until analysis by TLC indicated that the starting material had been consumed. The reaction mixture was filtered through a layer of CELITE filter aid and then concentrated under reduced pressure to provide 17 g of 4-[(3-aminoquinolin-4-yl)amino]butanol.

Part C

Triethyl orthopropionate (15.1 mL, 76.1 mmol, 1.1 eq.) and pyridine hydrochloride (catalytic amount) were added to a solution of 4-[(3-aminoquinolin-4-yl)amino]butanol (16 g, 69 mmol, 1 eq.) in pyridine (150 mL). The reaction mixture was heated at reflux for 1 hour at which time analysis by TLC indicated that all of the starting material had

been consumed. The reaction mixture was concentrated under reduced pressure. The residue was triturated with water (300 mL). The resulting solid was isolated by filtration, recrystallized from ethyl acetate, isolated by filtration, washed with cold ethyl acetate, and then air dried to provide 8.2 g of 4-(2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butanol as a solid.

Part D

Triphenylphosphine (3.35 g, 1.1 eq.) was added to a stirred suspension of 4-(2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butanol (3.13 g, 11.6 mmol, 1.0 eq.) in THF (50 mL). *N*-bromosuccinimide (2.28 g, 1.1 eq.) was added in portions over a period of ~ 1 min. After 45 minutes additional triphenylphosphine (0.2 eq.) and *N*-bromosuccinimide (0.2 eq.) were added. After an additional hour analysis by TLC indicated that the reaction was essentially complete. The reaction mixture was quenched with methanol (2 mL) and then concentrated under reduced pressure. The residue was dissolved in chloroform (200 mL), washed sequentially with water (50 mL), 5% sodium sulfite (50 mL), and brine (50 mL), dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by column chromatography (silica gel eluting with a gradient of 100% chloroform to 4/96 methanol/chloroform) to provide 3.07 g of 1-(4-bromobutyl)-2-ethyl-1*H*-imidazo[4,5-*c*]quinoline as an orange solid.

Part E

A suspension of the material from Part D (9.21 mmol, 1.0 eq.) was gently warmed until a solution was obtained. The solution was allowed to cool to near ambient temperature and then sodium hydrosulfide hydrate (671 mg, 1.3 eq.) was added in a single portion. The reaction mixture was stirred at ambient temperature over the weekend then warmed to 45 °C for 4 hours. The reaction mixture was cooled to ambient temperature overnight and then additional sodium hydrosulfide hydrate (0.3 eq.) was added. After 6 hours chloroform (10 mL) was added. The reaction mixture was stirred overnight and then concentrated under reduced pressure. The residue was combined with chloroform (175 mL), washed sequentially with water (2 x 50 mL) and brine (75 mL), dried over magnesium sulfate, and then concentrated under reduced pressure to provide 2.75 g of a pink foam. This material was purified by column chromatography (silica gel eluting with

a gradient of 3/97 to 4/96 methanol/chloroform) to provide 1.87 g of 4-(2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-thiol as a white foam.

Part F

A solution of sodium chlorate (103 mg, 1.3 eq.) in water (0.5 mL) was added dropwise with stirring to a chilled (0 °C) solution of 4-(2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-thiol (211 mg, 0.74 mmol, 1.0 eq.) in concentrated hydrochloric acid (1.0 mL). The reaction mixture was stirred for 1.5 hours. Chloroform (5 mL) was added followed by the addition of a solution of sodium dihydrogenphosphate (2.76 g, 23 mmol) in water (4 mL) to pH ~3. The reaction mixture was further diluted with water (20 mL) and chloroform (30 mL) and then aqueous saturated sodium bicarbonate was added with stirring until pH ~5. The layers were separated and the aqueous layer was extracted with chloroform (30 mL). The combined organics were dried over magnesium sulfate and then concentrated under reduced pressure to provide 190 mg of 4-(2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonyl chloride as a light yellow semisolid.

Part G

Dimethylamine (160 µL of 40% w/w in water, 2.4 eq.) was added to a stirred solution of the material from Part F (0.54 mmol, 1.0 eq.) in dichloromethane (5.4 mL). After 1 hour additional dimethylamine (1 eq) was added. The reaction mixture was allowed to stand over the weekend and then was concentrated under reduced pressure. The residue was diluted with chloroform (60 mL), washed sequentially with water (2 x 25 mL) and saturated sodium bicarbonate (25 mL), dried over magnesium sulfate, and then concentrated under reduced pressure to provide 138 mg of a yellow oil. The oil was combined with the material from another run and purified by column chromatography (silica gel eluting with 5/95 methanol/chloroform) to provide 222 mg of *N,N*-dimethyl 4-(2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide as a white foam.

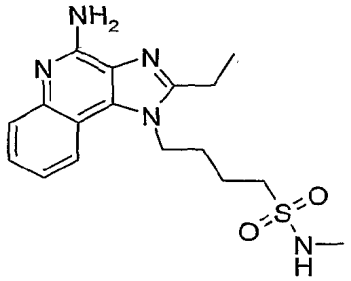
Part H

Using the general method of Example 2 Part F, the material from Part G was oxidized with 3-chloroperoxybenzoic acid (167 mg, 1.1 eq) and then aminated (3 mL concentrated ammonium hydroxide and 135 mg of tosyl chloride). The crude product was

purified by column chromatography (silica gel eluting with 5/95 methanol chloroform), triturated with ethyl acetate, and then dried under vacuum at 65 °C for 12 hours to provide 129 mg of *N,N*-dimethyl 4-(4-amino-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide as a white powder, mp 193-195°C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.05 (d, J=8.1 Hz, 1H), 7.60 (dd, J=1.2, 8.4 Hz, 1H), 7.41 (ddd, J=1.4, 7.1, 8.4 Hz, 1H), 7.25 (ddd, J=1.2, 7.1, 8.4 Hz, 1H), 6.43 (s, 2H), 4.56 (t, J=7.5 Hz, 2H), 3.10 (t, J=7.5 Hz, 2H), 2.96 (q, J-7.5 Hz, 2H), 2.73 (s, 6H), 1.88, (m, 4H), 1.38 (t, J=7.5 Hz, 3H); MS (APCI) *m/z*: 376 (M+H); Anal. calcd. for $C_{18}H_{25}N_5O_2S$: C, 57.58; H, 6.71; N, 18.65. Found: C, 57.54; H, 6.58; N, 18.65.

Example 4

N-Methyl 4-(4-amino-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide



Part A

Methylamine hydrochloride (504 mg, 2.1 eq.) was added to a stirred mixture of 4-(2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonyl chloride (1.25 g, 3.55 mmol, 1.0 eq.) and dichloromethane (36 mL). Aqueous potassium carbonate (1.30 mL of 6M, 2.2 eq.) was added. After 2 hours the reaction mixture was diluted with chloroform (100 mL), washed with brine (30 mL), dried over magnesium sulfate, and then concentrated under reduced pressure to provide 1.24 g of *N*-methyl 4-(2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide as a light brown solid.

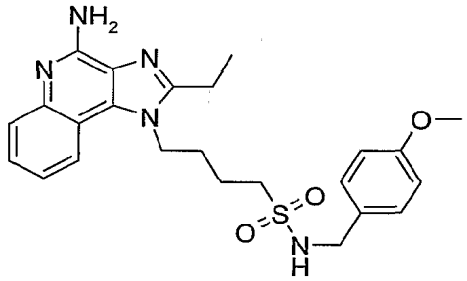
Part B

3-Chloroperoxybenozic acid (1.02 g of 77% max, 1.15 eq.) was added in a single portion to a stirred solution of the material from Part A (1.0 eq) in chloroform (36 mL). After 50 minutes concentrated ammonium hydroxide (8 mL) and tosyl chloride (819 mg,

1.2 eq.) were added. The reaction mixture was stirred for 2 hours and then the bulk of the chloroform was removed under reduced pressure. The residue was filtered, washed sequentially with water (10 mL) and isopropanol (2 x 8 mL), and then dried under vacuum to provide 722 mg of a tan solid. This material was recrystallized from 1,2-dichloroethane (~ 45 mL) then dried under vacuum at 50 °C for 18 hours to provide 491 mg of *N*-methyl 4-(4-amino-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide as an off-white powder, mp 190-191°C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.03 (d, J=8.4 Hz, 1H), 7.61 (dd, J=1.2, 8.4 Hz, 1H), 7.41 (ddd, J=1.2, 7.1, 8.3 Hz, 1H), 7.25 (ddd, J=1.2, 7.1, 8.3 Hz, 1H), 6.90 (q, J=4.8 Hz, 1H), 6.43 (br s, 2H), 4.54 (t, J=7.3 Hz, 2H), 3.08 (t, J=7.3 Hz, 2H), 2.96 (q, J=7.5 Hz, 2H), 2.54 (d, J=4.8 Hz, 3H), 1.94 (m, 2H), 1.81 (m, 2H), 1.38 (t, J=7.5 Hz, 3H); MS (APCI) *m/z*: 362 (M+H); Anal. calcd. for $C_{17}H_{23}N_5O_2S$•0.05 $C_2H_4Cl_2$: C, 56.05; H, 6.38; N, 19.11. Found: C, 55.83; H, 6.13; N, 18.92.

Example 5

N-(4-Methoxybenzyl) 4-(4-amino-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide



Part A

Aqueous potassium carbonate (0.35 mL of 6M, 1.2 eq.) was added to a stirred solution of 4-(2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonyl chloride (0.62 g, 1.76 mmol, 1.0 eq.) in dichloromethane (17 mL). 4-Methoxybenzylamine (0.25 mL, 1.1 eq.) was added dropwise and the reaction mixture was stirred for 2 hours. Additional aqueous potassium carbonate (1.2 eq.) and 4-methoxybenzylamine (1.1 eq.) were added and the reaction mixture was stirred over the weekend. The reaction mixture was diluted with chloroform (140 mL), washed with water (2 x 40 mL), dried over magnesium sulfate,

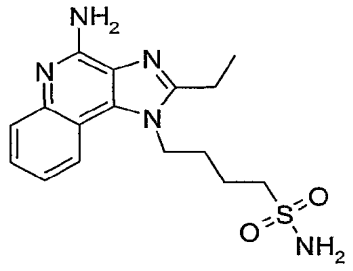
and then concentrated under reduced pressure to provide a brown oil. The oil was twice purified by column chromatography (silica gel eluting with 5/95 methanol/chloroform) to provide 412 mg of *N*-(4-methoxybenzyl) 4-(2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide as a white foam.

Part B

3-Chloroperoxybenzoic acid (257 mg of 77% max, 1.15 eq.) was added to a stirred solution of the material from Part A (1.0 eq) in chloroform (9.1 mL). After 1 hour concentrated ammonium hydroxide (3 mL) and tosyl chloride (207 mg, 1.2 eq.) were added. The reaction mixture was stirred vigorously for 20 hours, diluted with water (4 mL), and partially concentrated under reduced pressure. The residue was diluted with water (5 mL) and then extracted with chloroform (1 x 40 mL, then 4 x 20 mL). The combined extracts were dried over magnesium sulfate and then concentrated under reduced pressure to provide 0.47 g of a brown foam. The foam was purified by column chromatography (silica gel eluting with 25/75 80/18/2 chloroform/methanol/ammonium hydroxide (CMA)/chloroform) to provide 0.20 g of a tan foam. This material was reconcentrated from hot ethyl acetate/diethyl ether, recrystallized from ethanol, isolated by filtration, rinsed with ethanol (2 x 2 mL), and dried under vacuum at 80°C for 24 hours to provide 80 mg of *N*-(4-methoxybenzyl) 4-(4-amino-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide as a white powder, mp 176-177°C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.00 (d, J=8.1 Hz, 1H), 7.61 (dd, J=1.1, 8.3 Hz, 1H), 7.56 (t, J=5.9 Hz, 1H),7.42 (ddd, J=1.1, 7.2, 8.3 Hz, 1H), 7.25 (m, 3H), 6.84 (m, 2H), 6.43 (br s, 2H), 4.48 (t, J=7.6 Hz, 2H), 4.03 (d, J=5.9 Hz, 2H), 3.67 (s, 3H), 2.93 (m, 4H), 1.80 (m, 4H), 1.38 (t, J=7.5 Hz, 3H); MS (APCI) *m/z*: 468 (M+H); Anal. calcd. for $C_{24}H_{29}N_5O_3S$•0.05 EtOH, C, 61.60; H, 6.28; N, 14.90. Found: C, 61.39; H, 6.53; N, 14.84.

Example 6

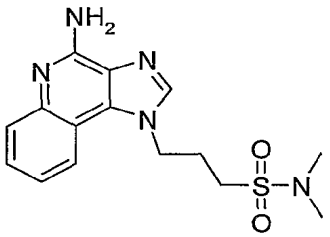
4-(4-Amino-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide



N-(4-Methoxybenzyl) 4-(4-amino-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide (180 mg) was dissolved in trifluoroacetic acid (3 mL) and stirred for 5.5 hours. The reaction mixture was concentrated under reduced pressure. The residue was suspended in methanol (15 mL) and then concentrated under reduced pressure. The residue was triturated with methanol (~ 3 mL), isolated by filtration, rinsed with methanol (2 mL), and then dried under vacuum to provide 168 mg of a white solid. This solid was triturated with hot dichloromethane (~ 3 mL), isolated by filtration, washed with dichloromethane(2 x 2 mL), and then dried under vacuum to provide 124 mg of a solid. This material was recrystallized from methanol (~ 8 mL evaporated to ~ 3 mL) to provide 67 mg of 4-(4-amino-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide trifluoroacetate as a white powder, mp 225-227°C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.43 (br s, 1H), 8.89 (br, 2H), 8.24 (d, J=8.1 Hz, 1H), 7.83 (d, J=8.4 Hz, 1H), 7.72 (t, J=8.0 Hz, 1H), 7.58 (dd, J=1.2, 8.3 Hz, 1H), 6.80 (br s, 2H), 4.62 (t, J=7.3 Hz, 2H), 3.05 (m, 4H), 1.92 (m, 4H), 1.41 (t, J=7.3 Hz, 3H); MS (APCI) *m/z*: 348 (M+H); Anal. calcd. for $C_{16}H_{21}N_5O_2S \cdot CF_3CO_2H$: C, 46.85; H, 4.81; N, 15.18. Found: C, 46.65; H, 4.82; N, 15.07.

Example 7

N,N-Dimethyl 3-(4-amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propane-1-sulfonamide



Part A

A solution of sodium dithionite (4.12 g of 85%, 5.0 eq.) in water (16 mL) was added dropwise to a stirred solution of *N,N*-dimethyl 3-[(3-nitroquinolin-4-yl)amino]propane-1-sulfonamide (1.60 g, 4.72 mmol, 1.0 eq.) in 1/1 acetonitrile/methanol (48 mL). A white precipitate formed during the addition. The reaction mixture was stirred vigorously for 1 hour and then filtered. The filter cake was rinsed with methanol (2 x 20 mL). The filtrate was concentrated under reduced pressure and then dried under vacuum overnight to provide 4.1 g of crude *N,N*-dimethyl 3-[(3-aminoquinolin-4-yl)amino]propane-1-sulfonamide as a yellow/orange solid.

Part B

Trimethyl orthoformate (0.62 mL, 1.2 eq.) and pyridine hydrochloride (55 mg, 0.1 eq.) were added sequentially to a stirred suspension of the material from Part A (1.0 eq.) in pyridine. The reaction was heated to 100 °C and stirred for 2 hours. Additional trimethyl orthoformate (1.2 eq.) was added and the reaction mixture was heated for an additional 6 hours. The reaction mixture was allowed to cool to ambient temperature overnight; analysis by TLC indicated that the reaction was complete. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between dichloromethane (100 mL) and water (75 mL). The aqueous layer was back extracted with dichloromethane (50 mL). The combined organics were dried over magnesium sulfate and concentrated under reduced pressure *N,N*-dimethyl 4-(2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide to provide a yellow foam. This material was purified by HPFC (silica gel eluting sequentially with 0-10% methanol in chloroform for 10 column volumes and 10% methanol in chloroform for 5 column volumes). The

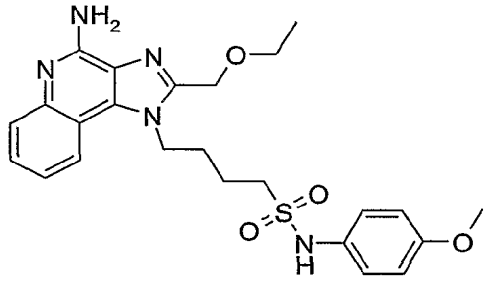
resulting material was reconcentrated from acetonitrile then dried under vacuum overnight to provide 1.26 g of *N,N*-dimethyl 3-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)propane-1-sulfonamide as an orange foam.

Part C

3-Chloroperoxybenozic acid (1.17 g of 77% max, 1.2 eq.) was added to a stirred solution of the material from Part B (1.0 eq) in chloroform (20 mL). After 1 hour concentrated ammonium hydroxide (2 mL) and tosyl chloride (943 mg, 1.25 eq.) were added with vigorous stirring. A white precipitate formed after 10 minutes; analysis by TLC indicated that the reaction was complete. After 1 hour the reaction mixture was filtered and the filter cake was rinsed with chloroform (2 x 15 mL). The filtrate was washed with water (20 mL). The aqueous was back extracted with chloroform (2 x 25 mL). The combined organics were dried over magnesium sulfate and concentrated under reduced pressure to provide 1.5 g of a brown foam. The foam was triturated with methanol (10 - 15 mL), isolated by filtration, rinsed with methanol (3 x 4 mL), and dried under vacuum at 100 °C to provide 435 mg of a white solid. This material was slurried with methanol (3 mL) containing several drops of 10% aqueous sodium hydroxide, isolated by filtration, rinsed with methanol (2 x 2 mL), and dried under vacuum [0.10 Torr (13 Pa)] at 110 °C for 6 hours to provide 330 mg of *N*-methyl 3-(4-amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propane-1-sulfonamide as a white powder, mp 155-157°C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.19 (s, 1H), 8.11 (d, J=7.5 Hz, 1H), 7.63 (dd, J=8.3, 0.8 Hz, 1H), 7.46 (m, 1H), 7.27 (m, 1H), 6.59 (br s, 2H), 4.72 (t, J=7.2 Hz, 2H), 3.19 (t, J=7.6 Hz, 2H), 2.74 (s, 6H), 2.27 (pentet, J=7.4 Hz, 2H); MS (APCI) *m/z* 334 $(M+H)^+$; Anal. calcd for $C_{15}H_{19}N_5O_2S$: C, 54.04; H, 5.74; N, 21.01. Found: C, 53.71; H, 6.06; N, 20.96.

Example 8

N-(4-Methoxyphenyl) 4-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide



Part A

A solution of thionyl chloride (49.6 g, 1.1 eq.) in dichloromethane (100 mL) was added dropwise with stirring to a chilled (0 °) suspension of 4-[(3-nitroquinolin-4-yl)amino]butanol (99 g, 379 mmol, 1 eq.) in dichloromethane (900 mL). The reaction mixture was stirred at ambient temperature overnight and then the pH was adjusted to pH 10 by adding aqueous potassium carbonate (6M). The layers were separated and the aqueous layer was extracted with dichloromethane (4 x 100 mL). The combined organics were washed with brine, dried over magnesium sulfate, and then concentrated under reduced pressure to provide crude product. This material was purified by chromatography (silica gel eluting with 7% methanol in dichloromethane to provide ~96 g of *N*-(4-chlorobutyl)-3-nitroquinolin-4-amine.

Part B

A solution of sodium dithionite (3.00 g, 5.0 eq) in water (11 mL) was added dropwise to a stirred suspension of *N*-(4-chlorobutyl)-3-nitroquinolin-4-amine (964 mg, 3.45 mmol, 1.0 eq.) in ethanol (34 mL). A precipitate formed during the addition. After 45 minutes the reaction mixture was filtered and the filter cake was rinsed with ethanol (3 x 12 mL). The filtrate was concentrated under reduced pressure and the residue was partitioned between dichloromethane (150 mL) and 50% sodium bicarbonate (60 mL). The organic layer was washed with 50% sodium bicarbonate (60 mL), dried over magnesium sulfate, and then concentrated under reduced pressure to provide 0.45 g of N^4-(4-chlorobutyl)quinoline-3,4-diamine as a yellow semisolid.

Part C

Ethoxyacetyl chloride (243 mg, 1.1. eq.) was added dropwise with stirring to a chilled (0 °) solution of the material from Part B (1.0 eq.) in dichloromethane (9 mL). The reaction mixture was stirred for 5 minutes then allowed to warm to ambient temperature and stirred for 1 hour. The reaction mixture was concentrated under reduced pressure to provide crude *N*-[4-(4-chlorobutyl)aminoquinolin-3-yl]-2-ethoxyacetamide hydrochloride as a yellow oil.

Part D

Aqueous sodium hydroxide (1.28 mL of 2M, 1.5 eq.) was added to a stirred solution of the material from Part C (1.0 eq.) in ethanol (17 mL). The reaction mixture was heated at 60-70 °C for 30 minutes at which time analysis by high performance liquid chromatography (HPLC) indicated that the reaction was complete. The reaction mixture was allowed to cool to ambient temperature over the weekend and then concentrated under reduced pressure. The residue was combined with material from another run and then partitioned between ethyl acetate (120 mL) and water (40 mL). The organic layer was dried over magnesium sulfate and concentrated under reduced pressure to provide 0.55 g of a yellow oil. This material was purified by HPFC (silica gel eluting with a gradient from 100% ethyl acetate to 10% methanol in ethyl acetate) to provide 1-(4-chlorobutyl)-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline as a yellow oil.

Part E

Potassium thioacetate (2.95 g, 1.1 eq.) was added in a single portion to a stirred solution of 1-(4-chlorobutyl)-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline (7.46 g, 23.5 mmol, 1.0 eq.) in DMF (110 mL). The solution was stirred overnight at ambient temperature and then concentrated under reduced pressure. The residue was dissolved in dichloromethane (200 mL), washed sequentially with water (100 mL) and brine (100 mL), dried over magnesium sulfate, and concentrated under reduced pressure to provide 8.06 g of product as a brown solid. The solid was further purified by washing with water and stirring over activated charcoal to provide S-[4-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl] thioacetate.

Part F

A stirred solution of S-[4-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl] thioacetate (4.19 g, 11.7 mmol, 1.0 eq.) in methanol (59 mL) was degassed with nitrogen for several minutes. Sodium methoxide (5.90 mL of 25 wt% in methanol, 2.2 eq.) was added and the reaction mixture was degassed for several more minutes. After 1 hour the reaction mixture was concentrated under reduced pressure. The residue was diluted with dichloromethane (150 mL) and water (50 mL); then hydrochloric acid (2M) was added to pH ~7. The layers were separated and the aqueous layer was back extracted with dichloromethane (50 mL). The combined organics were dried over magnesium sulfate and concentrated under reduced pressure to provide 3.72 g of crude product as a yellow oil. This oil was purified by HPFC (silica gel eluting with 0-20% CMA in chloroform for 5 column volumes and then with 20% CMA in chloroform for 5 column volumes) to provide 2.20 g of 4-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-thiol as a yellow oil.

Part G

A solution of sodium chlorate (965 mg, 1.3 eq.) was added dropwise with stirring to a chilled (0 °C) solution of the material from Part F (1.0 eq.) in hydrochloric acid (17 mL of 7M). The reaction mixture was allowed to stir for 90 minutes and then dichloromethane (100 mL) was added. Aqueous potassium carbonate (10 mL of 6M) was added dropwise. The reaction mixture was allowed to warm to ambient temperature and then it was poured into a mixture of dichloromethane (100 mL) and water (50 mL). The pH was adjusted to pH 4 by the addition of aqueous potassium carbonate (6M). The layers were separated and the aqueous layer was back extracted with dichloromethane (50 mL). The combined organics were dried over magnesium sulfate and concentrated under reduced pressure to provide 2.04 g of 4-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonyl chloride as a yellow foam.

Part H

4-Anisidine (689 mg, 1.2 eq.) was added to a stirred solution of 4-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonyl chloride (1.78 g, 4.66

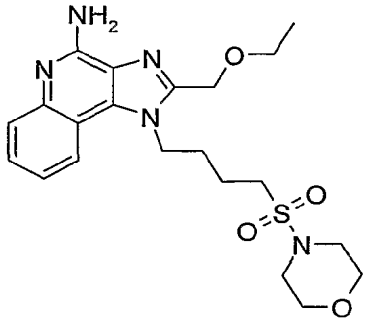
mmol, 1.0 eq.) in pyridine (15 mL). The reaction mixture was stirred at ambient temperature for 1 hour and then concentrated under reduced pressure. The residue was dissolved in dichloromethane (350 mL), washed sequentially with water (2 x 100 mL) and brine (100 mL), dried over magnesium sulfate and concentrated under reduced pressure to provide 1.90 g of crude product as a red oil. The oil was purified by HPFC (silica gel eluting with 0-20% CMA in chloroform for 5 column volumes and then with 20% CMA in chloroform for 7 column volumes) to provide 1.19 g of *N*-(4-methoxyphenyl) 4-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide as a tan solid.

Part I

3-Chloroperoxybenozic acid (622 mg of 77% max, 1.2 eq.) was added to a stirred solution of *N*-(4-methoxyphenyl) 4-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide (986 mg, 2.10 mmol,1.0 eq) in chloroform (21 mL). After 45 minutes analysis by TLC indicated that the oxidation was complete. Concentrated ammonium hydroxide (2 mL) and tosyl chloride (943 mg, 1.25 eq.) were added with vigorous stirring. After 30 minutes analysis by TLC indicated that the reaction was complete. After 1 hour the reaction mixture was partitioned between chloroform (200 mL) and water (60 mL). The aqueous layer was back extracted with chloroform (50 mL). The combined organics were dried over magnesium sulfate and concentrated under reduced pressure to provide 1.38 g of crude product as a brown foam. This material was purified by HPFC (silica gel eluting with 0-25% CMA in chloroform for 12 column volumes and then with 25% CMA in chloroform for 6 column volumes) followed by trituration with chloroform to provide 207 mg of a white solid. This material was dissolved in hot 9/1 methanol/chloroform (400 mL) and then concentrated under reduced pressure to provide 130 mg of *N*-(4-methoxyphenyl) 4-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide as a tan powder, mp 229-230°C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.48 (br s, 1H), 8.01 (d, J=7.9 Hz, 1H), 7.61 (dd, J=1.0, 8.3 Hz, 1H), 7.45 (m, 1H), 7.25 (m, 1H), 7.10 (m, 2H), 6.85 (m, 2H), 6.61 (br s, 2H), 4.75 (s, 2H), 4.57 (t, J=6.8 Hz, 2H), 3.70 (s, 3H), 3.52 (q, J=7.0 Hz, 2H), 3.03 (m, 2H), 1.87 (m, 4H), 1.11 (t, J=7.0 Hz, 3H); MS (APCI) *m/z* 484 $(M+H)^+$; Anal. calcd for $C_{24}H_{29}N_5O_4S$: C, 59.61; H, 6.04; N, 14.48. Found: C, 59.43; H, 6.41; N, 14.31.

Example 9

2-Ethoxymethyl-1-[4-(4-morpholine-4-sulfonyl)butyl]-1*H*-imidazo[4,5-*c*]quinoline-4-amine



Part A

Morpholine (0.54 mL, 1.2 eq.) was added to a stirred solution of 4-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonyl chloride (1.95 g, 5.0 mmol, 1.0 eq.) in pyridine (20 mL). The reaction mixture was stirred at ambient temperature for 1.5 hours and then concentrated under reduced pressure. The residue was dissolved in dichloromethane (300 mL) and washed with aqueous 50% sodium bicarbonate. The aqueous layer was back extracted with dichloromethane (100 mL). The combined organics were dried over magnesium sulfate and concentrated under reduced pressure to provide 1.39 g of crude product as a brown oil. The oil was purified by HPFC (silica gel eluting with 0-20% CMA in chloroform for 8 column volumes and then with 20% CMA in chloroform for 5 column volumes) to provide 1.05 g of 2-ethoxymethyl-1-[4-(4-morpholine-4-sulfonyl)butyl]-1*H*-imidazo[4,5-*c*]quinoline as a light yellow foam.

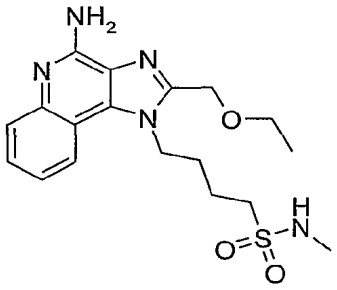
Part B

3-Chloroperoxybenozic acid (711 mg of 77% max, 1.2 eq.) was added to a stirred solution of the material from Part A (1.0 eq) in chloroform (24 mL). After 45 minutes concentrated ammonium hydroxide (2.4 mL) and tosyl chloride (573 mg, 1.25 eq.) were added with vigorous stirring. After 10 minutes analysis by TLC indicated that the reaction was complete. After 1 hour the reaction mixture was partitioned between chloroform (100 mL) and water (50 mL) containing 10% sodium hydroxide (3 mL), aqueous pH ~11. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure

to provide 1.7 g of crude product as a brown foam. This material was purified by HPFC (silica gel eluting with 0-20% CMA in chloroform for 12 column volumes and then with 20% CMA in chloroform for 6 column volumes) followed by trituration with ethyl acetate to provide 695 mg of a white solid. This material was dissolved in chloroform (200 mL), washed with 10% sodium hydroxide (~15 mL), dried over magnesium sulfate, and concentrated under reduced pressure. The residue was triturated with 10% sodium hydroxide, isolated by filtration, washed with water (2 x 4 mL), and dried under vacuum to provide 624 mg of a tan solid. This material was purified by HPFC (silica gel eluting with 10-20% CMA in chloroform for 5 column volumes and then with 20% CMA in chloroform for 7 column volumes) to provide 410 mg of a white solid. This material was triturated with ethyl acetate (~7 mL), isolated by filtration, rinsed with ethyl acetate (2 x 2 mL), and dried under vacuum [0.10 Torr, (13 Pa)] at 60°C over the weekend to provide 365 mg of 2-ethoxymethyl-1-[4-(4-morpholine-4-sulfonyl)butyl]-1*H*-imidazo[4,5-*c*]quinoline-4-amine as a white powder, 206-208°C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.08 (d, J=7.8 Hz, 1H), 7.62 (dd, J=1.0, 8.3 Hz, 1H), 7.45 (m, 1H), 7.27 (m, 1H), 6.59 (br s, 2H), 4.78 (s, 2H), 4.63 (t, J=7.3 Hz, 2H), 3.59 (m, 6H), 3.13 (m, 6H), 2.00 (m, 2H), 1.87 (m, 2H), 1.18 (t, J=7.0 Hz, 3H); MS (APCI) *m/z* 448 $(M+H)^+$; Anal. calcd for $C_{21}H_{29}N_5O_4S$: C, 56.36; H, 6.53; N, 15.65. Found: C, 56.13; H, 6.62; N, 15.47.

Example 10

N-Methyl 4-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide



Part A

Methylamine hydrochloride (2.2 eq) was added to a mixture of 4-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonyl chloride (2 g, 5.23 mmol, 1 eq.) and

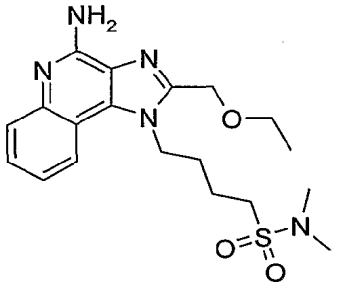
dichloromethane (20 mL). Aqueous potassium carbonate (2 mL of 6M, 2.2 eq.) was added and the reaction mixture was stirred overnight. The reaction mixture was diluted with water (10 mL). The organic layer was separated, washed sequentially with water (2 x 10 mL) and brine, dried over magnesium sulfate, and concentrated under reduced pressure to provide 1.39 g of *N*-methyl 4-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide.

Part B

3-Chloroperoxybenzoic acid (1.08 g of 65%, 1.1 eq.) was added in portions to a solution of the material from Part A in dichloromethane (15 mL). After 45 minutes concentrated ammonium hydroxide (5 mL) was added. Tosyl chloride (1.58 g, 1.1 eq.) was added in portions and the reaction mixture was allowed to stir for 2 hours. The pH was adjusted to pH 8 by the addition of hydrochloric acid (6M). The reaction mixture was filtered to remove solids. The organic layer was concentrated under reduced pressure to provide 2 g of crude product as a black oil. This material was purified by chromatography. The residue was recrystallized from toluene containing activated charcoal then dried under vacuum with heating to provide 0.18 g of *N*-methyl 4-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide as yellow granules, mp 170.0-172.0 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 8.06 (d, J = 7.6 Hz, 1H), 7.61 (dd, J = 8.2, 0.9 Hz, 1H), 7.45 (m, 1H), 7.27 (m, 1H), 6.89 (q, J = 4.9 Hz, 1H), 6.58 (s, 2H), 4.78 (s, 2H), 4.60 (t, J = 7.5 Hz, 2H), 3.57 (q, J = 7.0 Hz, 2H), 3.07 (t, J = 7.5 Hz, 2H), 2.56 (d, J = 4.9 Hz, 3H), 1.98 (m, 2H), 1.84 (m, 2H), 1.17 (t, J = 7.0 Hz, 3H); MS (APCI) *m/z* 392 $(M + H)^+$; Anal. Calcd for $C_{18}H_{25}N_5O_3S$: C, 55.22; H, 6.44; N, 17.89. Found: C, 55.16; H, 6.56; N, 17.78.

Example 11

N,N-Dimethyl 4-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide



Part A

Dimethylamine hydrochloride (0.65 g, 2.2 eq) was added to a mixture of 4-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonyl chloride (1.4 g, 3.6 mmol, 1 eq.) and dichloromethane (15 mL). Aqueous potassium carbonate (2 mL of 6M, 2.2 eq.) was added and the reaction mixture was stirred overnight. The reaction mixture was diluted with water (10 mL). The organic layer was separated, washed sequentially with water (2 x 10 mL) and brine, dried over magnesium sulfate, and concentrated under reduced pressure to provide 1.26 g of *N,N*-dimethyl 4-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide.

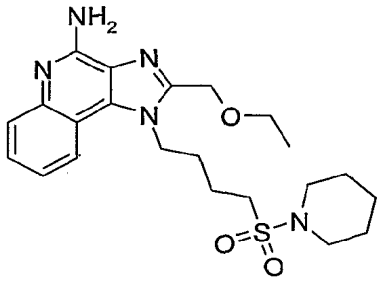
Part B

3-Chloroperoxybenzoic acid (1.23 g of 65%, 1.1 eq.) was added in portions to a solution of the material from Part A in dichloromethane (16 mL). After 30 minutes additional 3-chloroperoxybenzoic acid (0.1 g) was added and the reaction mixture was allowed to stir overnight. Concentrated ammonium hydroxide (5 mL) was added. Tosyl chloride (4.9 g, 1.1 eq.) was added in portions and the reaction mixture was allowed to stir for 2 hours. The reaction mixture was diluted with water (100 mL) and dichloromethane (50 mL). The organic layer was separated and concentrated under reduced pressure to provide 2.6 g of crude product as a brown oil. This material was purified by chromatography (silica gel eluting with 5% methanol in dichloromethane). The product was further purified by HPFC (silica gel eluting with 5% methanol in ethyl acetate) to provide 0.3 g of a solid. This material was recrystallized from toluene and then dissolved

in hot methanol. The methanol was removed under vacuum to provide 0.17 g of *N,N*-dimethyl 4-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide as a light yellow powder, mp 173.0-174.0 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 8.07 (d, J = 7.4 Hz, 1H), 7.62 (dd, J = 8.3, 1.1 Hz, 1H), 7.45 (m, 1H), 7.27 (m, 1H), 6.59 (s, 2H), 4.78 (s, 2H), 4.62 (t, J = 7.5 Hz, 2H), 3.57 (q, J = 7.0 Hz, 2H), 3.09 (t, J = 7.5 Hz, 2H), 2.74 (s, 6H), 1.99 (m, 2H), 1.86 (m, 2H), 1.17 (t, J = 6.9 Hz, 3H); MS (APCI) *m/z* 406 $(M + H)^+$; Anal. Calcd for $C_{19}H_{27}N_5O_3S$: C, 56.28; H, 6.71; N, 17.27. Found: C, 55.90; H, 6.44; N, 17.17.

Example 12

2-Ethoxymethyl-1-[4-(piperidine-1-sulfonyl)butyl]-1*H*-imidazo[4,5-*c*]quinoline-4-amine



Part A

Piperidine (0.71 mL, 1.1 eq.) was added to a mixture of 4-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonyl chloride (2.5 g, 6.5 mmol, 1 eq.) and dichloromethane (25 mL). Aqueous potassium carbonate (2 mL of 6M, 2.2 eq.) was added and the reaction mixture was stirred for 2 days. The organic layer was separated and concentrated under reduced pressure to provide 2.4 g of crude product as a brown oil. The oil was purified by HPFC (silica gel eluting with 10% CMA in chloroform) to provide 2 g of 2-ethoxymethyl-1-[4-(piperidine-1-sulfonyl)butyl]-1*H*-imidazo[4,5-*c*]quinoline.

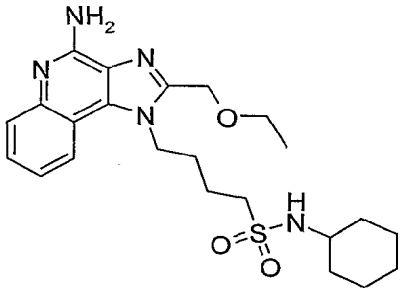
Part B

3-Chloroperoxybenzoic acid (1.35 g of 65%, 1.1. eq.) was added to a solution of the material from Part A (1.0 eq.) in chloroform (20 mL). The reaction mixture was stirred until analysis by HPLC indicated that the oxidation was complete. Concentrated ammonium hydroxide (6 mL) was added and a precipitate formed. Tosyl chloride (1.05 g,

1.2 eq.) was added in portions with vigorous stirring. The reaction mixture was stirred until analysis indicated that it was complete. The reaction mixture was diluted with dichloromethane (50 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3 x 30 mL). The combined organics were washed sequentially with water and brine, dried over magnesium sulfate, and concentrated under reduced pressure to provide 0.6 g of a brown oil. The oil was purified by HPFC (silica gel eluting with a gradient of 10-18% CMA in chloroform, 1200 mL total) followed by recrystallization from 1,2-dichloroethane to provide 80 mg of 2-ethoxymethyl-1-[4-(piperidine-1-sulfonyl)butyl]-1*H*-imidazo[4,5-*c*]quinoline-4-amine as a white powder, mp 185.0 -188.0°C. ^{1}H NMR (300 MHz, DMSO d_6) δ 8.07 (d, J = 7.7 Hz, 1H), 7.61 (dd, J = 8.3, 1.1 Hz, 1H), 7.45 (m, 1H), 7.26 (m, 1H), 6.61 (s, 2H), 4.78 (s, 2H), 4.62 (t, J = 7.3 Hz, 2H), 3.57 (q, J = 7.0 Hz, 2H), 3.08 (m, 6H), 1.98 (m, 2H), 1.84 (m, 2H), 1.48 (m, 6H), 1.17 (t, J = 7.0 Hz, 3H); MS (APCI) *m/z* 446 $(M + H)^+$; Anal. Calcd for $C_{22}H_{31}N_5O_3S$: C, 59.30; H, 7.01; N, 15.72. Found: C, 59.05; H, 7.35; N, 15.62.

Example 13

N-Cyclohexyl 4-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide



Part A

Cyclohexylamine (1.48 g, 2.2 eq.) was added to a mixture of 4-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonyl chloride (2.6 g, 6.8 mmol, 1 eq.) and dichloromethane (25 mL). Aqueous potassium carbonate (2 mL of 6M, 2.2 eq.) was added and the reaction mixture was stirred for 2 hours. The reaction mixture was diluted with water (10 mL) and dichloromethane (25 mL). The organic layer was separated, washed sequentially with water (2 x 10 mL) and brine, dried over magnesium sulfate, and

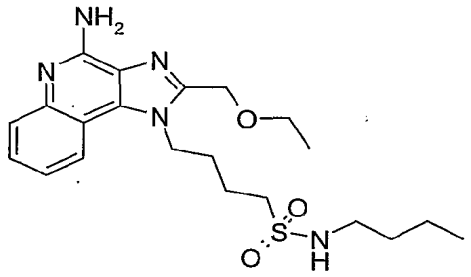
concentrated under reduced pressure. The residue was purified by HPFC (silica gel eluting with 2% methanol in chloroform) to provide 2 g of *N*-cyclohexyl 4-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide.

Part B

3-Chloroperoxybenzoic acid (2 g of 65%, 1.1. eq.) was added to a solution of the material from Part A (1.0 eq.) in dichloromethane (20 mL). The reaction mixture was stirred for 1 hour. Concentrated ammonium hydroxide (6 mL) was added. Tosyl chloride (1.03 g, 1.2 eq.) was added in portions with vigorous stirring and the reaction mixture was allowed to stir for 4 hours. The pH was adjusted to pH 8 by the addition of hydrochloric acid (6M). The reaction mixture was filtered to remove solids. The organic layer was concentrated under reduced pressure to provide 2.2 g of crude product as a light brown oil. The oil was purified by HPFC (silica gel eluting with 3% CMA in chloroform) followed by recrystallization from ethanol to provide 0.88 g of *N*-cyclohexyl 4-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide as a light yellow powder, mp 197.0-198.0 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 8.04 (d, J = 7.8 Hz, 1H), 7.62 (dd, J = 8.2, 0.9 Hz, 1H), 7.45 (dd, J = 7.8, 0.7, Hz, 1H), 7.26 (dd, J = 8.0, 1.0 Hz, 1H), 7.03 (d, J = 7.6 Hz, 1H), 6.59 (s, 2H), 4.78 (s, 2H), 4.60 (t, J = 7.4 Hz, 2H), 3.56 (q, J = 7.0 Hz, 2H), 3.04 (t, J = 7.5 Hz, 3H), 1.98 (m, 2H), 1.79 (m, 4H), 1.63 (m, 2H), 1.50 (m, 1H), 1.17 (t, J = 6.9 Hz, 3H), 1.13 (m, 5H); MS (APCI) *m/z* 460 $(M + H)^+$; Anal. Calcd for $C_{23}H_{33}N_5O_3S$: C, 60.11; H, 7.24; N, 15.24. Found: C, 59.83; H, 7.07; N, 15.06.

Example 14

N-Butyl 4-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide



Part A

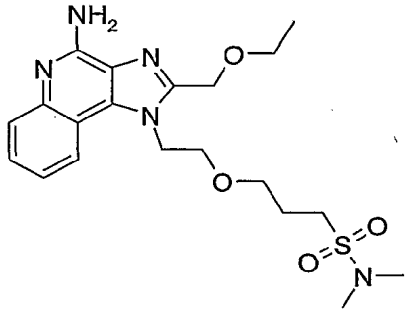
Butylamine (0.71 mL, 1.1 eq.) was added to a mixture of 4-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonyl chloride (2.5 g, 6.5 mmol, 1 eq.) and dichloromethane (25 mL). Aqueous potassium carbonate (2.0 mL of 6M, 2.2 eq.) was added and the reaction mixture was stirred overnight. The organic layer was decanted away from the salts and concentrated under reduced pressure. The residue was purified by HPFC (silica gel eluting with 2% methanol in chloroform) to provide 2 g of *N*-butyl 4-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide.

Part B

3-Chloroperoxybenzoic acid (1.39 g of 65%, 1.1. eq.) was added to a solution of the material from Part A (1.0 eq.) in chloroform (20 mL). The reaction mixture was stirred for 2 hours then additional 3-chloroperoxybenzoic acid (0.1 eq.) was added and the reaction mixture was stirred overnight. Concentrated ammonium hydroxide (6 mL) was added and a precipitate formed. Tosyl chloride (1.14 g, 1.2 eq.) was added in portions with vigorous stirring. The reaction mixture was stirred for 4 hours and then diluted with dichloromethane (60 mL) and water (20 mL). The organic layer was washed sequentially with 10% sodium hydroxide and brine, dried over magnesium sulfate, and concentrated under reduced pressure to provide 1.8 g of crude product as a foam. The foam was purified by HPFC (silica gel eluting with 14% CMA in chloroform) to provide a pale yellow solid. This material was recrystallized from ethanol and dried under vacuum at 50 °C for 4 hours to provide 0.6 g of *N*-butyl 4-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide as a white powder, mp 148.0-149.0 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 8.05 (d, J = 8.0 Hz, 1H), 7.61 (dd, J = 8.3, 1.0 Hz, 1H), 7.45 (m, 1H), 7.27 (m, 1H), 7.02 (t, J = 5.9 Hz, 1H), 6.61 (br s, 2H), 4.78 (s, 2H), 4.60 (t, J = 7.5 Hz, 2H), 3.56 (q, J = 7.0 Hz, 2H), 3.05 (t, J = 7.5 Hz, 2H), 2.88 (q, J = 6.5 Hz, 2H), 1.97 (m, 2H), 1.84 (m, 2H), 1.40 (m, 2H), 1.29 (m, 2H), 1.17 (t, J = 7.0 Hz, 3H), 0.85 (t, J = 7.2 Hz, 3H); MS (APCI) *m/z* 434 $(M + H)^+$; Anal. Calcd for $C_{21}H_{31}N_5O_3S$: C, 58.17; H, 7.21; N, 16.15. Found: C, 58.23; H, 7.28; N, 16.16.

Example 15

N,N-Dimethyl 3-[2-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]propane-1-sulfonamide



Part A

Triethylamine (46.8 mL, 3.5 eq.) and 4-chloro-3-nitroquinoline (20.0 g, 95.9 mmol, 1.0 eq) were added sequentially to a stirred mixture of 3-(2-aminoethoxy)propanol (29.9 g, 2.0 eq.) and dichloromethane (320 mL). The reaction mixture was stirred for 1 hour at which time analysis by TLC showed that all of the starting material had been consumed. The reaction mixture was diluted with dichloromethane (250 mL) and washed with water (300 mL). The organic layer was dried over magnesium sulfate and concentrated under reduced pressure to provide 32 g of crude product as a yellow oil. The oil was dissolved in chloroform and filtered through a plug of silica gel (300 g) eluting sequentially with chloroform (100 mL) and 2/98 methanol/chloroform (2 L) to provide 25.78 g of 3-{2-[(3-nitroquinolin-4-yl)amino]ethoxy}propanol as a yellow solid.

Part B

Thionyl chloride (3.43 mL, 1.1. eq.)) was added dropwise to a mixture of 3-{2-[(3-nitroquinolin-4-yl)amino]ethoxy}propanol (12.46 g, 42.77 mmol, 1.0 eq.) in dichloromethane (143 mL). A solution resulted and it was stirred for 20 hours. The reaction mixture was diluted with dichloromethane (250 mL) and then quenched with 50% sodium bicarbonate (~250 mL). The organic layer was dried over magnesium sulfate and concentrated under reduced pressure to provide 9.39 g of *N*-[2-(3-chloropropoxy)ethyl]-3-nitroquinolin-4-amine as a yellow oil which slowly solidified.

Part C

Acetonitrile (50 mL) was added with stirring to a suspension of the material from Part B (1.0 eq.) in warm ethanol (100 mL) to provide a solution. A solution of sodium dithionite (26.30 g of 85%, 5.0 eq.) in water (100 mL) was added. An exotherm was observed (37 °C) and a white precipitate formed. The reaction mixture was stirred vigorously for 30 minutes and then filtered. The filter cake was washed with acetonitrile (2 x 30 mL). The filtrate was concentrated under reduced pressure. The residue was partitioned between dichloromethane (350 mL) and aqueous saturated sodium bicarbonate (200 mL); aqueous pH ~7). The aqueous was back extracted with dichloromethane (4 x 75 mL). The combined organics were dried over magnesium sulfate and concentrated under reduced pressure to provide 7.28 g of N^4-[2-(3-chloropropoxy)ethyl]quinoline-3,4-diamine as a yellow oil.

Part D

Ethoxyacetyl chloride (2.93 mL, 1.1 eq.) was added dropwise to a stirred solution of the material from Part C (1.0 eq.) in dichloromethane (130 mL). After 1 hour the reaction mixture was concentrated under reduced pressure to provide *N*-{4-[2-(3-chloropropoxy)ethylamino]quinoline-3-yl}-2-ethxoyacetamide as a yellow foam.

Part E

Sodium hydroxide (19.5 mL of 2M, 1.5 eq.) was added to a stirred solution of the material from Part D in ethanol (130 mL). The reaction mixture was warmed to 50 °C and stirred for 1.5 hours at which time analysis by TLC indicated that the reaction was complete. The reaction mixture was cooled to ambient temperature and then concentrated under reduced pressure. The residue was partitioned between dichloromethane (250 mL) and water (75 mL). The aqueous was back extracted with dichloromethane (50 mL). The combined organics were washed with brine (50 mL), dried over magnesium sulfate, and concentrated under reduced pressure to provide 8.40 g of crude product as an oil. The oil was purified by HPFC (silica gel eluting with 0-20% CMA in chloroform for 5 column volumes and then 20% CMA in chloroform for 4 column volumes) to provide 7.64 g of 1-[2-(3-chloropropoxy)ethyl]-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline as a yellow oil.

Part F

Potassium thioacetate (1.01 g, 1.1 eq.) was added to a stirred solution of 1-[2-(3-chloropropoxy)ethyl]-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline (2.80 g, 8.05 mmol, 1.0 eq.) in DMF (16 mL). The resulting suspension was stirred vigorously overnight. Additional potassium thioacetate (0.1 eq.) was added and the reaction mixture was stirred for another 2 hours. The reaction mixture was concentrated under reduced pressure. The residue was diluted with dichloromethane (250 mL) and washed sequentially with water (75 mL) and brine (100 mL). The organic layer was dried over magnesium sulfate and concentrated under reduced pressure to provide 3.07 g of S-{3-[2-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy}propyl thioacetate as a light yellow solid.

Part G

A stirred solution of the material from Part F (1.0 eq.) in methanol (40 mL) was degassed with nitrogen for a few minutes. Sodium methoxide (4.0 mL of 25 wt% in methanol, 2.2 eq.) was added and the degassing was continued for a few more minutes. After 1 hour the reaction mixture was concentrated under reduced pressure. The residue was diluted with dichloromethane (200 mL) and water (100 mL) and the pH was adjusted to pH~7 with 2M hydrochloric acid. The layers were separated and the aqueous layer was back extracted with dichloromethane (50 mL). The combined organics were dried over magnesium sulfate and concentrated under reduced pressure to provide 2.80 g of crude product as a yellow oil. The oil was purified by HPFC (silica gel eluting with 0-20% CMA in chloroform over 5 column volumes then with 20% CMA in chloroform for 5 column volumes) to provide 2.39 g of 3-[2-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]propane-1-thiol as a yellow oil.

Part H

A solution of sodium chlorate (953 mg, 1.3 eq.) in water (1.5 mL) was added dropwise over a period of ~30 seconds to a chilled (0 °C) solution of the material from Part G (1.0 eq) in hydrochloric acid (17 mL of 7M). The reaction mixture was stirred for 90 minutes and then degassed with nitrogen for a few minutes. Dichloromethane (60 mL) was added followed by the dropwise addition of aqueous potassium carbonate (10 mL of 6M). The reaction mixture was allowed to warm to ambient; the aqueous layer was pH~2.

The reaction mixture was poured into dichloromethane (150 mL) and water (60 mL) and the pH was adjusted to pH 4 with 6M potassium carbonate. The layers were separated and the aqueous layer was back extracted with dichloromethane (50 mL). The combined organics were dried over magnesium sulfate and concentrated under reduced pressure to provide 2.25 g of 3-[2-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]propane-1-sulfonyl chloride as a light yellow oil.

Part I

Dimethylamine hydrochloride (935 mg, 2.1 eq.) was added to a stirred solution of the material from Part H (1.0 eq.) in dichloromethane (27 mL). Aqueous potassium carbonate (2.0 mL of 6M, 2.2 eq.) was added and a white precipitate formed. Analysis by TLC indicated that the reaction was complete in 10 minutes. After 1 hour the reaction mixture was diluted with dichloromethane (125 mL) and washed with water (40 mL). The organic layer was dried over magnesium sulfate and concentrated under reduced pressure to provide 2.03 g of crude product as a yellow oil. The oil was purified by HPFC (silica gel eluting with 0-20% CMA in chloroform over 9 column volumes then with 20% CMA in chloroform for 4 column volumes) to provide 1.46 g of *N,N*-dimethyl 3-[2-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline-1-yl)ethoxy]propane-1-sulfonamide as a yellow oil.

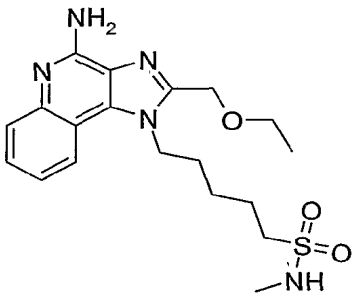
Part J

3-Chloroperoxybenzoic acid (1.02 g of 70%, 1.2 eq.) was added to a stirred solution of the material from Part I in chloroform (17 mL). After 1 hour concentrated ammonium hydroxide (3 mL) and tosyl chloride (822 mg, 1.25 eq.) were added sequentially with vigorous stirring. After 10 minutes analysis by TLC indicated that the reaction was nearly complete. After 1 hour the reaction mixture was partitioned between chloroform (100 mL) and water (50 mL) containing 10% sodium hydroxide (3 mL); aqueous pH ~11. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure to provide 1.7 g of crude product as a brown foam. The foam was purified by HPFC (silica gel eluting with 0-20% CMA in chloroform over 12 column volumes then with 20% CMA in chloroform over 6 column volumes) to provide 0.847 g of a light brown foam. The foam was warmed in hexanes (~15-20 mL) until the foam

started to melt. An equal volume of dichloromethane was added with swirling until solids formed. The mixture was triturated until all of the oily material was solidified. The solids were isolated by filtration, rinsed with 3/1 hexanes/ dichloromethane (2 x 3 mL), and dried under vacuum [0.1 Torr (13 Pa.)] at 40 °C for 3 days to provide 614 mg of *N,N*-dimethyl 3-[2-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline-1-yl)ethoxy]propane-1-sulfonamide as a white powder, mp 61-64°C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.13 (d, J=7.6 Hz, 1H), 7.61 (dd, J=1.0, 8.3 Hz, 1H), 7.44 (m, 1H), 7.24 (m, 1H), 6.57 (br s, 2H), 4.83 (t, J=5.3 Hz, 2H), 4.79 (s, 2H), 3.87 (t, J=5.4 Hz, 2H), 3.56 (q, J=7.0 Hz, 2H), 3.42 (t, J=6.1 Hz, 2H), 2.79 (m, 2H), 2.63 (s, 6H), 1.75 (m, 2H), 1.17 (t, J=7.0 Hz, 3H); MS (APCI) *m/z* 436 $(M+H)^+$; Anal. calcd for $C_{20}H_{29}N_5O_4S$: C, 55.15; H, 6.71; N, 16.08. Found: C, 54.94; H, 7.00; N, 16.00.

Example 16

N-Methyl 5-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentane-1-sulfonamide



Part A

Triethylamine (26.68 g, 1.1 eq.) was added to a suspension of 4-chloro-3-nitroquinoline (50 g, 240 mmol, 1.0 eq.) in dichloromethane (500 mL) and all of the solids dissolved. A solution of 5-aminopentanol (27.2 g, 1.1 eq.) in dichloromethane (100 mL) was added dropwise over a period of 30 minutes. The reaction mixture was stirred overnight and then concentrated under reduced pressure to a volume of ~200 mL. Ice water was added and the mixture was triturated for about an hour. Hydrochloric acid (10 %) was added to lower the pH from 10 to ~7 and a precipitate formed. The mixture was stirred for about 1 hour. The solid was isolated by filtration and air dried to provide 59 g of 5-[(3-nitroquinolin-4-yl)amino]pentanol.

Part B

A solution of thionyl chloride (20 mL, 1.1 eq) in dichloromethane (50 mL) was added dropwise with stirring to a chilled (0 °C) suspension of 5-[(3-nitroquinolin-4-yl)amino]pentanol (50.4 g, 183 mmol,1.0 eq.) in dichloromethane (300 mL). The reaction mixture was stirred for 3 hours and then filtered to remove solids. The pH of the filtrate was adjusted to 7-8 with aqueous 5% sodium carbonate. The layers were separated. The aqueous layer was back extracted with dichloromethane (6 x 20 mL). The combined organics were washed sequentially with water and brine, dried over magnesium sulfate, and concentrated under reduced pressure to provide 47.4 g of *N*-(5-chloropentyl)-3-nitroquinolin-4-amine.

Part C

A mixture of the material from Part B, catalyst (5% platinum on carbon), and acetonitrile (1.5 L) was hydrogenated on a Parr apparatus until analysis by TLC indicated that the reaction was complete. The reaction mixture was filtered to remove the catalyst and the filtrate was concentrated under reduced pressure to provide 39.8 g of N^4-(5-chloropentyl)quinoline-3,4-diamine as a yellow brown oil.

Part D

Ethoxyacetyl chloride (21.66 g, 1.1 eq.) was added dropwise over a period of 15 minutes to a chilled (0 °C) solution of the material from Part C (1.0 eq.) in dichloromethane (400 mL). The reaction mixture was allowed to warm to ambient temperature overnight and then was concentrated under reduced pressure to provide 51.7 g of *N*-[4-(5-chloropentyl)aminoquinolin-3-yl]-2-ethoxyacetamide.

Part E

A solution of the material from Part D (1.0 eq.) in ethanol and sodium hydroxide (82 mL of 2M) was heated to 60 °C. After 4 hours analysis by HPLC indicated that the reaction was complete and the reaction mixture was concentrated under reduced pressure. The residue was combined with dichloromethane (200 mL) and then filtered to remove

solids. The filtrate was concentrated under reduced pressure to provide 45.1 g of 1-(5-chloropentyl)-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline as a dark oil.

Part F

A mixture of the material from Part E (1.0 eq.), potassium thioacetate (18.2 g, 1.1 eq.), and DMF (100 mL) was stirred at ambient temperature overnight. The reaction mixture was partitioned between dichloromethane (300 mL) and cold water (100 mL). The organic layer was washed with water (8 x 100 mL). The combined aqueous was back extracted with dichloromethane (50 mL). The combined organics were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by eluting through a plug of silica gel to provide 50 g of S-[5-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline-1-yl)pentyl] thioacetate as a brown oil.

Part G

A solution of S-[5-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentyl] thioacetate (6.4 g, 17.2 mmol, 1.0 eq.) in methanol (50 mL) was degassed with nitrogen for about 20 minutes. Sodium methoxide (4.1 g of 25 wt% in methanol, 1.1 eq.) was diluted with methanol (20 mL) and similarly degassed. The two solutions were combined and stirred for 1 hour at which time analysis by HPLC indicated that all of the starting material had been consumed. The reaction mixture was concentrated under reduced pressure. The residue was diluted with dichloromethane (50 mL) and water (30 mL) and the pH was adjusted to pH 8 with 6M hydrochloric acid. The layers were separated and the aqueous layer was back extracted with dichloromethane (20 mL). The combined organics were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure to provide 5.9 g of 5-[2-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]pentane-1-thiol as a yellow green oil.

Part H

A solution of sodium chlorate (1.67 g, 1.3 eq.) in water (3 mL) was added dropwise to a chilled solution of 5-[2-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]pentane-1-thiol (4 g, 12 mmol, 1.0 eq.) in hydrochloric acid (50 mL of 6N). After about an hour the reaction mixture was diluted with dichloromethane (120 ml) and

then potassium carbonate was added to adjust the aqueous to pH 6. The organic layer was concentrated under reduced pressure to provide 3.5 g of 5-[2-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]pentane-1-sulfonyl chloride.

Part I

A mixture of the material from Part H (1 eq), methylamine hydrochloride (1.5 g, 2.2.eq.), potassium carbonate (1.53 g, 2.2 eq.) and dichloromethane was stirred overnight. Additional methylamine hydrochloride (1 eq.) and potassium carbonate (1 eq.) were added and the reaction mixture was stirred overnight. The reaction mixture was combined with that from another run and then diluted with sufficient water to dissolve the salts that were present. The organic layer was concentrated under reduced pressure to provide 3.65 g of *N*-methyl 5-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentane-1-sulfonamide as an oil.

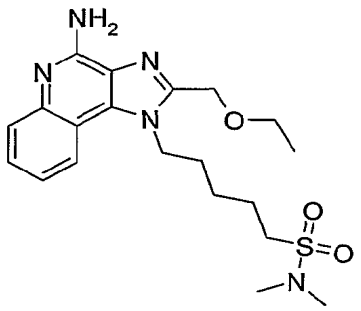
Part J

3-Chloroperoxybenzoic acid (2.61 g of 65%, 1.1 eq.) was added in portions to a stirred solution of the material from Part I (1 eq.) in dichloromethane (20 mL). After 2 hours additional 3-chloroperoxybenzoic acid (0.6 eq) was added and the reaction mixture was stirred for 45 minutes. The reaction mixture was diluted with water (15 mL). The aqueous layer was back extracted with dichloromethane (5 mL). The combined organics were washed with brine, dried over magnesium sulfate, and then concentrated under reduced pressure. Ammonium hydroxide (5 mL of 18M) was added to the residue. Tosyl chloride (2.04 g, 1.2 eq.) was added in portions and the reaction mixture was stirred overnight. The reaction mixture was diluted with dichloromethane (100 mL). The aqueous layer was back extracted with dichloromethane (20 mL). The combined organics were washed sequentially with water and brine, dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide a tan solid. The solid was recrystallized from toluene, isolated by filtration, rinsed with toluene, and dried under vacuum overnight to provide 1.7 g of *N*-methyl 5-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentane-1-sulfonamide as yellow granules, mp 175.0-179.0°C. ^{1}H NMR (300 MHz, DMSO d_6) δ 8.02 (d, J = 8.0 Hz, 1H), 7.62 (dd, J = 8.3, 0.7 Hz, 1H), 7.45 (t, J = 7.5 Hz, 1H), 7.28 (m, 1H), 6.85 (q, J = 4.9 Hz, 1H), 6.60 (s, 2H), 4.78

(s, 2H), 4.56 (t, J = 7.5 Hz, 2H), 3.56 (q, J = 6.9 Hz, 2H), 3.01 (t, J = 7.5 Hz, 2H), 2.54 (d, J = 4.8 Hz, 3H), 1.89 (m, 2H), 1.70 (m, 2H), 1.58 (m, 2H), 1.16 (t, J = 6.9 Hz, 3H); MS (APCI) *m/z* 406 $(M + H)^+$; Anal. Calcd for $C_{19}H_{27}N_5O_3S$: C, 56.28; H, 6.71; N, 17.27. Found: C, 55.97; H, 6.78; N, 17.10.

Example 17

N,N-Dimethyl 5-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentane-1-sulfonamide



Part A

Dimethylamine hydrochloride (1.61 g, 2.2 eq.) and a solution of potassium carbonate (1.36 g, 2.2 eq) in water (1 mL) were added sequentially to a solution of 5-[2-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]pentane-1-sulfonyl chloride (3.5 g, 8.9 mmol, 1 eq) in dichloromethane (60 mL). The reaction mixture was stirred overnight and then diluted with water (10 mL). The organic layer was washed with water and then concentrated under reduced pressure to provide 3.6 g of *N,N*-dimethyl 5-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentane-1-sulfonamide.

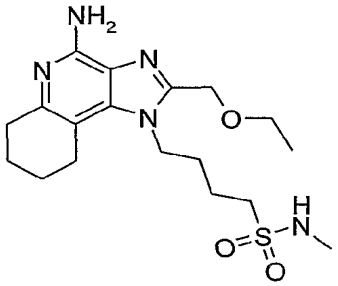
Part B

3-Chloroperoxybenzoic acid (2.38 g of 65%, 1.1 eq.) was added in portions to a stirred solution of the material from Part A (1 eq.) in dichloromethane (20 mL). After 3 hours the reaction mixture was diluted with water (15 mL). The aqueous layer was back extracted with dichloromethane (5 mL). The combined organics were washed with brine, dried over magnesium sulfate, and then concentrated under reduced pressure. Ammonium hydroxide (5 mL of 18M) was added to the residue. Tosyl chloride (1.86 g, 1.2 eq.) was added in portions and the reaction mixture was stirred overnight. The reaction mixture

was diluted with dichloromethane (100 mL). The aqueous layer was back extracted with dichloromethane (20 mL). The combined organics were washed sequentially with water and brine, dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide a tan solid. The solid was recrystallized from toluene, isolated by filtration, rinsed with toluene, and dried under vacuum overnight to provide 1.7 g of *N,N*-dimethyl 5-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentane-1-sulfonamide as a white powder, mp 138.0-142.0°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (dd, J = 8.3, 0.7 Hz, 1H), 7.82 (dd, J = 8.2, 0.7 Hz, 1H), 7.53 (ddd, J = 8.3, 7.2, 1.2 Hz, 1H), 7.35 (m, 1H), 5.38 (s, 2H), 4.80 (s, 2H), 4.59 (t, J = 7.8 Hz, 2H), 3.62 (q, J = 7.0 Hz, 2H), 2.90 (t, J = 7.5 Hz, 2H), 2.85 (s, 6H), 2.04 (m, 2H), 1.91 (m, 2H), 1.67 (m, 2H), 1.25 (s, J = 6.9 Hz, 3H); MS (APCI) *m/z* 420 $(M + H)^+$; Anal. Calcd for $C_{20}H_{29}N_5O_3S$: C, 57.26; H, 6.97; N, 16.69. Found: C, 57.10; H, 7.10; N, 16.58.

Example 18

N-Methyl 4-(4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide

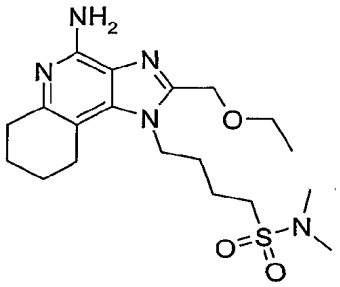


A solution of *N*-methyl 4-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide (1.01 g, 2.5 mmol) in trifluoroacetic acid (2 mL) was combined with a catalytic amount of platinum(IV) oxide and hydrogenated on a Parr apparatus until analysis by HPLC/mass spectroscopy indicated that the reaction was complete. The reaction mixture was filtered through a layer of CELITE filter aid. The filter cake was rinsed with fresh trifluoroacetic acid and the filtrate was concentrated under reduced pressure to provide 0.8 g of crude product as a dark oil. The oil was suspended in hydrochloric acid (5 mL) and stirred for about 1 hour. The pH was adjusted to about 7 with 10% sodium hydroxide. The resulting solid was isolated by filtration, recrystallized from ethanol and then dried under high vacuum at about 78 °C to provide 0.4 g of *N*-

methyl 4-(4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide, mp 188 – 192 °C. Anal. calcd. for $C_{18}H_{29}N_5O_3S$: C, 54.66; H, 7.39; N, 17.71. Found: C, 54.42; H, 7.39; N, 17.52.

Example 19

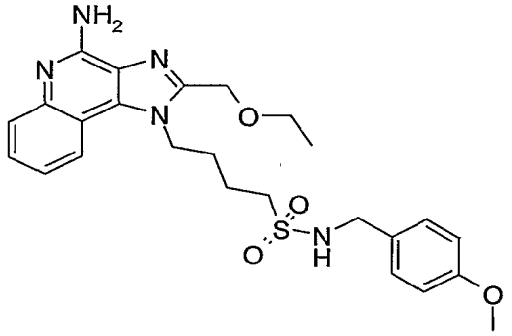
N,N-Dimethyl 4-(4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide



A mixture of *N,N*-dimethyl 4-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide (1.25 g, 3.0 mmol), trifluoroacetic acid (10 mL) and platinum(IV) oxide (1.22 g) was hydrogenated on a Parr apparatus until analysis by LC/mass spectroscopy indicated that the reaction was complete. The reaction mixture was filtered through a layer of CELITE filter aid. The filter cake was rinsed with fresh trifluoroacetic acid (2 mL) and chloroform (20 mL) and the filtrate was concentrated under reduced pressure to provide crude product as an oil. The oil was dissolved in concentrated hydrochloric acid (5 mL) and stirred overnight. The solution was neutralized with 6M potassium carbonate (6 mL), diluted with dichloromethane (25 mL), adjusted to pH 13 with 10% sodium hydroxide, and then stirred for about 2 hours. The organic layer was separated and concentrated under reduced pressure. The residue (0.7 g) was purified by chromatography (silica gel eluting with a gradient of 13 % CMA in chloroform to 28% CMA in chloroform over 10.6 column volumes) to provide 0.6 g of a white solid. The white solid was recrystallized from methanol, isolated by filtration, and then dried under high vacuum to provide 0.4 g of *N,N*-dimethyl 4-(4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide as white needles, mp 165-167 °C. Anal. calcd. for $C_{19}H_{31}N_5O_3S$: C, 55.72; H, 7.63; N, 17.10. Found: C, 55.84; H, 7.54; N, 17.19.

Example 20

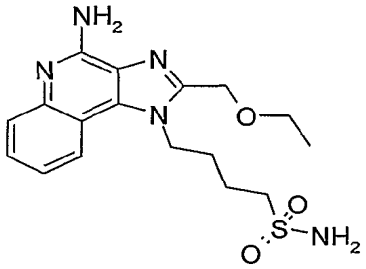
N-(4-Methoxybenzyl) 4-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide



The general procedure of Example 14 was repeated using 4-methoxybenzylamine in lieu of butylamine to provide *N*-(4-methoxybenzyl) 4-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide, mp 101 °C. Anal. calcd. for $C_{25}H_{31}N_5O_4S \cdot 0.59\ H_2O$: C, 59.08; H, 6.38; N, 13.78; Found: C, 59.21; H, 6.74; N, 13.59.

Example 21

4-(4-Amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide

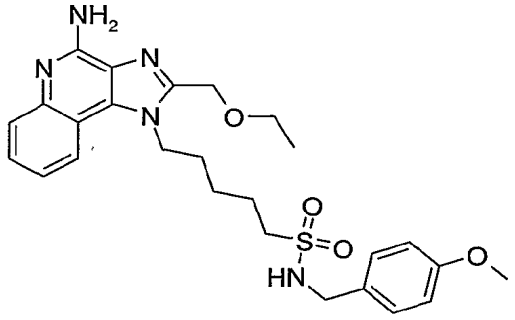


A solution of *N*-(4-methoxybenzyl) 4-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide (0.81 g) in trifluoroacetic acid (5 mL) was stirred at ambient temperature until analysis by LC/mass spectroscopy indicated that all of the starting material had been consumed. The reaction mixture was concentrated under reduced pressure and then placed under high vacuum. The residue was suspended in concentrated hydrochloric acid (5 mL) and stirred for about 1 hr. The resulting solid was isolated by filtration, recrystallized from methanol, isolated by filtration, and then dried under high vacuum at 78 °C to provide 0.28 g of 4-(4-amino-2-ethoxymethyl-1*H*-

imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide, mp 155-158 °C. Anal. calcd. for $C_{17}H_{23}N_5O_3S$: C, 54.09; H, 6.14; N, 18.55 Found: C, 53.86; H, 6.13; N, 18.24.

Example 22

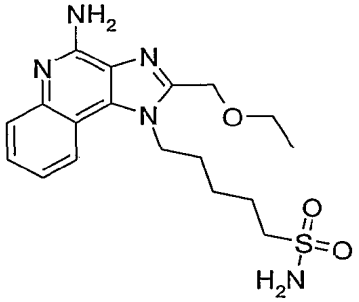
N-(4-Methoxybenzyl) 5-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentane-1-sulfonamide



The general procedure of Example 16 Parts I and J was repeated using 4-methoxybenzylamine in lieu of methylamine to provide *N*-(4-methoxybenzyl) 5-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentane-1-sulfonamide, mp 177-178 °C. Anal. calcd. for $C_{26}H_{33}N_5O_4S$: C, 61.04; H, 6.50; N, 13.69 Found: C, 61.07; H, 6.74; N, 13.77.

Example 23

5-(4-Amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentane-1-sulfonamide

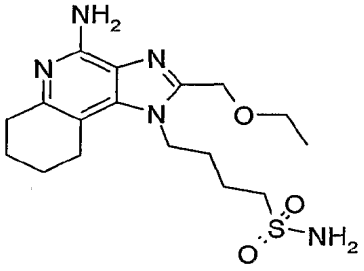


A solution of *N*-(4-methoxybenzyl) 5-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentane-1-sulfonamide (2.3 g) in trifluoroacetic acid (~ 20 g) was stirred overnight. A portion (~ 8 mL) was concentrated under reduced pressure. The residue was partitioned between 6M hydrochloric acid (9 mL) and dichloromethane (30 mL). The

aqueous layer was chilled in an ice bath and 10% sodium hydroxide was added with stirring to pH 13. The mixture was stirred for about 1 hr and then the pH was adjusted to 7. The resulting precipitate was isolated by filtration, recrystallized from methanol, isolated by filtration, and then dried under high vacuum at 78 °C to provide 0.5 g of 5-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentane-1-sulfonamide, mp 176-178 °C. Anal. calcd. for $C_{18}H_{25}N_5O_3S$: C, 55.22; H, 6.44; N, 17.89 Found: C, 55.06; H, 6.42; N, 17.84.

Example 24

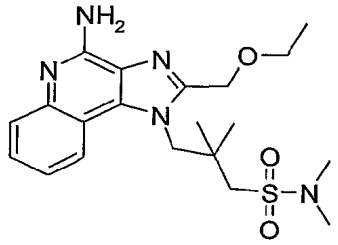
4-(4-Amino-2-ethoxymethyl-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide



A solution of *N*-(4-methoxybenzyl) 4-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide (0.6 g) in trifluoroacetic acid was stirred at ambient temperature until analysis by LC/mass spectroscopy indicated that all of the starting material had been consumed. The solution was combined with platinum (IV) oxide and hydrogenated on a Parr apparatus until analysis by LC/mass spectroscopy indicated that the reaction was complete. The reaction mixture was filtered through a layer of CELITE filter aid. The filter cake was rinsed with fresh trifluoroacetic acid and the filtrate was concentrated under reduced pressure to provide the trifluoroacetate of the product as an oil. This material was converted to the free base using the general method of Example 23, recrystallized sequentially from methanol and then water, and then dried under high vacuum at 91 °C to provide 4-(4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide, mp 224-227 °C. Anal. calcd. for $C_{17}H_{27}N_5O_3S$: C, 53.52; H, 7.13; N, 18.36 Found: C, 53.36; H, 7.24; N, 18.06.

Example 25

N,N-Dimethyl 3-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropane-1-sulfonamide



Part A

Triethylamine (17.5 mL, 1.3 eq) was added dropwise to a suspension of 4-chloro-3-nitroquinoline (20.14 g, 96.5 mmol, 1.0 eq) in dichloromethane (300 mL). 3-Amino-2,2-dimethylpropanol (10.96 g, 1.1 eq) was added, the reaction mixture was stirred for 45 minutes and then concentrated under reduced pressure. The residue was slurried with water (300 mL) for 1 hr, isolated by filtration, rinsed with water (2 x 60 mL), and then dried under high vacuum to provide 20.7 g of 2,2-dimethyl-3-[(3-nitroquinolin-4-yl)amino]propanol as a yellow solid.

Part B

A suspension of 2,2-dimethyl-3-[(3-nitroquinolin-4-yl)amino]propanol (1.45 g) and 10% palladium on carbon in ethanol was hydrogenated on a Parr apparatus until analysis by TLC indicated that the reaction was complete. The reaction mixture was filtered through a layer of CELITE filter aid. The filter cake was rinsed with ethanol (3 x 10 mL). The filtrate was concentrated under reduced pressure. The residue was suspended in toluene (150 mL) and concentrated under reduced pressure to provide 3-[(3-aminoquinolin-4-yl)amino]-2,2-dimethylpropanol.

Part C

Ethoxyacetyl chloride (564 µL, 1.05 eq) was added dropwise to a chilled (0 °C) solution of the material from Part B (1.0 eq) in pyridine (25 mL). The progress of the reaction was monitored by TLC, additional ethoxyacetyl chloride (0.6 eq) was added to drive the reaction to completion. The reaction mixture was allowed to warm to ambient

temperature overnight. The reaction mixture was heated at 80 °C for 2 hrs and then at 110 °C for 9 hours. The reaction mixture was cooled to ambient temperature and then concentrated under reduced pressure. The residue was combined with the material obtained from another run and then purified by HPFC (silica gel eluting with 0-40% acetone in chloroform (0.75% ethanol stabilized) over 1 L and then with 40 – 60 % acetone in chloroform over 1.8 L) to provide 1.66 g of 3-(2-ethoxymethyl-1*H*-imidazo[4,5-c]quinolin-1-yl)-2,2-dimethylpropanol as a clear oily semisolid.

Part D

Tosyl chloride (1.18 g, 1.2 eq) and 4-dimethylaminopyridine (13 mg, 0.02 eq) were added sequentially to a solution of 3-(2-ethoxymethyl-1*H*-imidazo[4,5-c]quinolin-1-yl)-2,2-dimethylpropanol (1.61 g, 5.14 mmol, 1.0 eq) in pyridine (6 mL). The reaction mixture was stirred at ambient temperature for 20 hrs, quenched with brine (75 mL), and then extracted with ethyl acetate (1 x 75 mL). The extract was dried over magnesium sulfate, filtered, and then concentrated under reduced pressure. The residue was dissolved in dichloromethane (20 mL), diluted with heptanes (125 mL), concentrated under reduced pressure, and then dried under high vacuum to provide 2.12 g of 3-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropyl *p*-toluenesulfonate as a light brown oil.

Part E

Sodium hydrosulfide hydrate (1.23 g, 5.0 eq) was added to a solution of the material from Part D (1.0 eq) in ethanol (22 mL). The reaction was heated at 75 °C for 30 hours and then allowed to cool to ambient temperature over the weekend. Analysis by TLC indicated that the reaction was not complete. Additional sodium hydrosulfide hydrate (3 eq) was added and the reaction mixture was heated for an additional 48 hrs. The reaction mixture was concentrated under reduced pressure. The residue was suspended in water (100 mL) and then extracted with dichloromethane (3 x 100 mL). The combined extracts were dried over magnesium sulfate and then concentrated under reduced pressure to provide 1.23 g of a white foam. This material was purified by HPFC (silica gel eluting with 0-10% CMA in chloroform over 2 column volumes, 10-25% CMA in chloroform over 7 column volumes, 25-35% CMA in chloroform over 1.5 column

volumes, and 35% CMA in chloroform over 5 column volumes) to provide 0.87 g of 3-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropane-1-thiol as a clear oil.

Part F

Using the general method of Example 8 Part G, 3-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropane-1-thiol (0.75 g) was oxidized to provide 0.67 g of 3-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropane-1-sulfonyl chloride as an oily yellow foam.

Part G

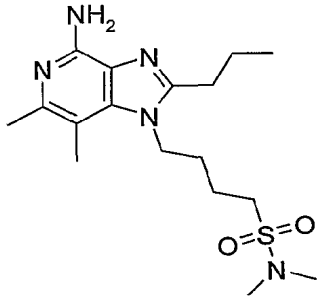
Using the general method of Example 11 Part A, the material from Part F was reacted with dimethylamine hydrochloride. The crude product was purified by HPFC (silica gel eluting with 0-30% CMA in chloroform for 8 column volumes and then 30% CMA in chloroform for 3 column volumes) to provide 0.36 g of *N,N*-dimethyl 3-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropane-1-sulfonamide as an off white foam.

Part H

Using the general method of Example 11 Part B, the material form Part G was oxidized and then aminated. The crude product was purified by (silica gel eluting with 0-30% CMA in chloroform for 15 column volumes and then 30% CMA in chloroform for 2 column volumes) to provide 0.19 g of a brown oil. The oil was dissolved in ethanol (8 mL), combined with 7 M hydrochloric acid (65 μL), stirred for 10 minutes and then concentrated to a sticky brown oil. The oil was triturated with hot ethyl acetate to provide a solid, concentrated, triturated with hot acetonitrile (6 – 7 mL), and then cooled to ambient temperature. The resulting solid was isolated by filtration, rinsed with acetonitrile (3 x 1 mL), and dried (0.10 Torr (13 Pa) at 50 °C for 3 days; then at 0.12 Torr (16 Pa) at 60 °C for 16 hrs) to provide 133 mg of the hydrochloride salt of *N,N*-dimethyl 3-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropane-1-sulfonamide as a tan powder, mp 193-195 °C. Anal. calcd. for $C_{20}H_{29}N_5O_3S \cdot HCl \cdot 0.15\ H_2O$: C, 52.37; H, 6.66; N, 15.27 Found: C, 52.07; H, 6.75; N, 15.08.

Example 26

N,N-Dimethyl 4-(4-Amino-6,7-dimethyl-2-propyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butane-1-sulfonamide



Part A

Under a nitrogen atmosphere, triethylamine (38 mL, 2.0 eq) was added in a single portion to a mixture of 2,4-dichloro-5,6-dimethyl-3-nitropyridine (30.0g, 136 mmol, 1.0 eq) and *N,N*-dimethylformamide (DMF, 450 mL). The reaction mixture was stirred for 10 minutes, 4-amino-1-butanol (17.6 mL, 1.4 eq) was added, and the reaction mixture was stirred overnight. The reaction mixture was concentrated under reduced pressure to provide crude product as an oil. The oil was partitioned between chloroform (500 mL) and water/brine (1:1 50 mL). The organic phase was separated, washed with water/brine (1:1 3 x 30 mL), dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide an orange solid. This material was dried under high vacuum at 40 °C and then recrystallized from ethyl acetate/hexanes to provide 23.0 g of 4-(2-chloro-5,6-dimethyl-3-nitropyridin-1-yl)butan-1-ol.

Part B

Under a nitrogen atmosphere, a mixture of 4-(2-chloro-5,6-dimethyl-3-nitropyridin-1-yl)butan-1-ol (24.5 g, 89.5 mmol, 1.0 eq), sodium azide (11.6 g, 2.0 eq.), cerium(III) chloride heptahydrate (16.7 g, 0.5 eq), and acetonitrile/water (9:1 250 mL) was heated at reflux overnight. The reaction mixture was filtered while still hot and the filter cake was rinsed with warm acetonitrile and DMF. The filtrate was concentrated under reduced pressure and then dried under high vacuum at 50 °C for 2 hrs to provide 25 g of crude 4-[(5,6-dimethyl-8-nitrotetraazolo[1,5-*a*]pyridin-7-yl)amino]butan-1-ol.

Part C

Under a nitrogen atmosphere, thionyl chloride (9.8 mL, 1.5 eq) was added dropwise with stirring to a mixture of the material from Part B and chloroform (500 mL). The reaction mixture was heated at a vigorous reflux for 3.5 hrs, cooled to ambient temperature, and then diluted with water (200 mL). The phases were separated and the aqueous phase was extracted with chloroform (3 x 100 mL). The combined organics were washed with water (3 x 50 mL), dried over magnesium sulfate, filtered, concentrated under reduced pressure, and then dried under high vacuum to provide 30 g of crude *N*-(4-chlorobutyl)-5,6-dimethyl-8-nitrotetraazolo[1,5-*a*]pyridin-7-amine as an orange oil.

Part D

The material from Part C was combined in a pressure vessel with catalyst (2.5 g of 5% platinum on carbon), and ethyl acetate (500 mL). The reaction mixture was placed under hydrogen pressure ((30 psi, (2.1 x 10^5 Pa)) for 2 days. Analysis by HPLC indicated that the reaction was not complete. More catalyst (~ 1.3 g) was added and the reaction was continued until analysis by HPLC indicated that the reaction was complete. The reaction mixture was filtered through a layer of CELITE filter aid and the filter cake was washed with chloroform. The filtrate was concentrated under reduced pressure to provide 20.0 g of N^7-(4-chlorobutyl)-5,6-dimethyltetraazolo[1,5-*a*]pyridine-7,8-diamine as an off white solid.

Part E

Under a nitrogen atmosphere, pyridine hydrochloride (1.62 g, 0.375 eq) and trimethyl orthobutyrate (6.5 mL, 1.1. eq) were added sequentially to a suspension of N^7-(4-chlorobutyl)-5,6-dimethyltetraazolo[1,5-*a*]pyridine-7,8-diamine (10.0 g, 37.2 mmol, 1 eq) in toluene (250 mL). The reaction mixture was heated at reflux for 1 hour, allowed to stand at ambient temperature over the weekend, and then concentrated under reduced pressure. The resulting white solid was partitioned between chloroform (400 mL) and saturated aqueous sodium bicarbonate (50 mL). The phases were separated and the aqueous phase was extracted with chloroform (2 x 20 mL). The combined organics were washed with saturated aqueous sodium bicarbonate (3 x 25 mL), dried over magnesium sulfate, filtered, concentrated under reduced pressure, and then dried under high vacuum to

provide 11.75 g of 7-(4-chlorobutyl)-5,6-dimethyl-8-propyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridine an off white solid.

Part F

A mixture of the material from Part E (1.0 eq), potassium thioacetate (4.6 g, 1.1 eq), and DMF (250 mL) was stirred under a nitrogen atmosphere overnight. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between chloroform (300 mL) and water/brine (1:1 100 mL). The phases were separated and the aqueous phase was extracted with chloroform (2 x 75 mL). The combined organics were washed with water/brine (1:1, 3 x 50 mL), dried over magnesium sulfate, filtered, concentrated under reduced pressure, and then dried under high vacuum with gentle heating to provide 13.0 g of S-[4-(5,6-dimethyl-8-propyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)butyl] thioacetate as a brown solid.

Part G

A solution of S-[4-(5,6-dimethyl-8-propyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)butyl] thioacetate (6.5 g, 18.0 mmol, 1.0 eq) in methanol (150 mL) was degassed with nitrogen for about 10 minutes. Sodium methoxide (10.3 mL of 25 wt% in methanol, 2.5 eq) was added dropwise over a period of 5 minutes. The solution was stirred at ambient temperature for 2 hrs and then concentrated under reduced pressure. The residue was partitioned between dichloromethane (300 mL) and water (50 mL). The pH was adjusted to 7 by the addition of 1N hydrochloric acid. The phases were separated and the aqueous phase was extracted with dichloromethane (2 x 75 mL). The combined organics were washed with brine (50 mL), dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide 4-(5,6-dimethyl-8-propyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)butane-1-thiol as a yellow solid.

Part H

Under a nitrogen atmosphere, the material from Part G (1.0 eq) was combined with concentrated hydrochloric acid (30 mL) and water (20 mL) and then cooled to 0°C. A solution of sodium chlorate (2.50 g, 1.3 eq) in water (10 mL) was added over a period of 10 minutes with vigorous stirring. The reaction mixture was stirred for 2 hrs at 0°C and

then diluted with dichloromethane (100 mL). The pH was adjusted to 7 by slowly adding 6M potassium carbonate (~ 30 mL). A white precipitate formed during the addition. The reaction mixture was diluted with dichloromethane (100 mL) and water (100 mL) and then allowed to warm to ambient temperature. The aqueous layer was separated and then extracted with dichloromethane (2 x 50 mL). The combined organics were dried over magnesium sulfate, filtered and then concentrated under reduced pressure to provide 2.6 g of 4-(5,6-dimethyl-8-propyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)butane-1-sulfonyl chloride as a yellow solid.

Part I

Under a nitrogen atmosphere, dimethylamine hydrochloride (1.16 g, 2.1 eq) was added to a suspension of the material from Part H (1.0 eq) in dichloromethane (65 mL). 6M potassium carbonate (2.81 mL, 2.5 eq) was added dropwise and the reaction mixture was stirred at ambient temperature for 2 hours. More dimethylamine hydrochloride (0.21 eq) and 6M potassium carbonate (0.25 eq) were added and the reaction mixture was stirred for 1 hr. The reaction mixture was diluted with dichloromethane (150 mL) and saturated aqueous sodium bicarbonate (75 mL) and the phases were separated. The aqueous phase was extracted with dichloromethane (3 x 50 mL). The combined organics were washed with aqueous sodium bicarbonate (2 x 50 mL), dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide crude product as a yellow foam. The crude product was purified by HPFC (silica gel eluting with 2-30% CMA in chloroform) to provide 0.8 g of *N,N* dimethyl 4-(5,6-dimethyl-8-propyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)butane-1-sulfonamide as a white solid.

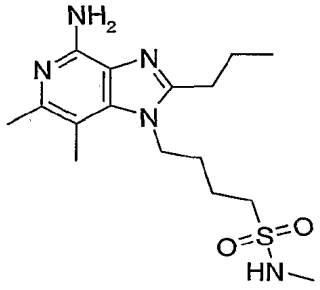
Part J

The material from Part I, platinum (IV) oxide (160 mg), and trifluoroacetic acid (20 mL) were combined in a pressure vessel and placed under hydrogen pressure (50 psi, 3.4 x 10^5 Pa) over the weekend. The reaction mixture was concentrated under reduced pressure. The residue was diluted with 1N hydrochloric acid (~ 10 mL) and then stirred at ambient temperature for 1 hr. The solution was cooled to 0 °C, the pH was adjusted to 7-8 by adding saturated aqueous sodium bicarbonate, and then it was extracted with chloroform (3 x 75 mL). The combined organics were washed with aqueous sodium

bicarbonate (3 x 40 mL), dried over sodium sulfate, filtered, concentrated under reduced pressure, and then dried under high vacuum to provide crude product. The crude product was recrystallized from ethyl acetate/hexanes, isolated by filtration, washed with ethyl acetate, and then dried under high vacuum overnight to provide 448 mg of *N,N*-dimethyl 4-(4-amino-6,7-dimethyl-2-propyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butane-1-sulfonamide as a white powder, mp 127.0-128.0 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.59 (s, 2H), 4.24 (dd, J = 7.2, 6.4 Hz, 2H), 3.09 (dd, J = 7.2, 6.8 Hz, 2H), 2.81-2.68 (m, 8H), 2.37 (s, 3H), 2.30 (s, 3H), 1.86-1.67 (m, 6H), 1.00 (t, J = 7.4 Hz, 3H); MS (APCI) *m/z* 368 $(M)^+$; Anal. calcd for $C_{17}H_{29}N_5O_2S$: C, 55.56; H, 7.95; N, 19.06; Found: C, 55.35; H, 8.08; N, 19.02.

Example 27

N-Methyl 4-(4-Amino-6,7-dimethyl-2-propyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butane-1-sulfonamide



Part A

Using the general method of Example 26 Part I, 4-(5,6-dimethyl-8-propyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)butane-1-sulfonyl chloride (2.0 g, 5.2 mmol, 1.0 eq) was reacted with methylamine hydrochloride (740 mg, 2.1 eq) to provide 1.86 g of N-methyl 4-(5,6-dimethyl-8-propyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)butane-1-sulfonamide.

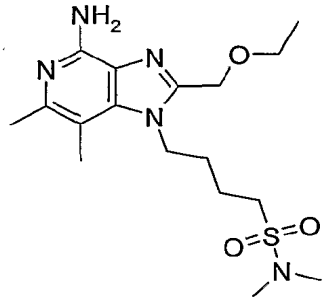
Part B

The material from Part A, platinum IV oxide (~ 500 mg), and trifluoroacetic acid (50 mL) were combined in a pressure vessel and placed under hydrogen pressure (50 psi, 3.4 x 10^5 Pa) until analysis by HPLC indicated that the reaction was complete. The

reaction mixture was filtered and the filter cake was washed with methanol. The filtrate was concentrated under reduced pressure. The residue was diluted with 1N hydrochloric acid (~ 10 mL) and then stirred at ambient temperature for 1 hr. The solution was cooled to 0 °C and the pH was adjusted to 7-8 by adding saturated aqueous sodium bicarbonate. A white precipitate formed. The precipitate was isolated by filtration, rinsed with water, and then dissolved in methanol. The methanol solution was filtered, diluted with toluene, concentrated under reduced pressure, and then dried under high vacuum to provide a white solid. The solid was triturated with ethyl acetate and methanol, isolated by filtration, washed sequentially with ethyl acetate, acetonitrile, chloroform, and ethyl acetate, and then dried under high vacuum. The material was then combined with 1N sodium hydroxide (5 mL), sonicated for 1 minute, and diluted with water (20 mL) and chloroform (100 mL). The phases were separated and the aqueous phase was extracted with chloroform (3 x 20 mL). The combined organics were washed with 1N sodium hydroxide. The combined aqueous were neutralized to pH 7 by the addition of 1N hydrochloric acid and then back extracted with chloroform (3 x 30 mL). The combined organics were dried over sodium sulfate, filtered, concentrated under reduced pressure, dried under high vacuum at 100 °C for 3 hrs, triturated sequentially with ethyl acetate and methanol, and then dried under high vacuum to provide 100 mg of *N*-methyl 4-(4-amino-6,7-dimethyl-2-propyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butane-1-sulfonamide as a white powder, mp 164.0-166.0 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.88 (q, J = 4.9 Hz, 1H), 5.72 (s, 2H), 4.23 (dd, J = 7.8, 6.3 Hz, 2H), 3.06 (dd, J = 7.6, 6.6 Hz, 2H), 2.77 (t, J = 7.4 Hz, 2H), 2.56 (d, J = 4.9 Hz, 3H), 2.37 (s, 3H), 2.31 (s, 3H), 1.86-1.65 (m, 6H), 1.00 (t, J = 7.4 Hz, 3H); MS (APCI) *m/z* 354 $(M)^+$; Anal. Calcd for $C_{16}H_{27}N_5O_2S$: C, 54.37; H, 7.699; N, 19.81; Found: C, 54.14; H, 7.76; N, 19.62.

Example 28

N,N-Dimethyl 4-(4-Amino-6,7-dimethyl-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butane-1-sulfonamide



Part A

Ethoxyacetyl chloride (3.93 g, 1.0 eq) was slowly added to a chilled (0 °C) suspension of N^7-(4-chlorobutyl)-5,6-dimethyltetraazolo[1,5-*a*]pyridine-7,8-diamine (7.93 g, 29.5 mmol, 1.0 eq) in dichloromethane (200 mL). The reaction mixture was allowed to warm to ambient temperature overnight. Analysis by HPLC indicated that the reaction was not complete. The reaction mixture was cooled to 0 °C, more ethoxyacetyl chloride (0.4 g) was added, and then the reaction mixture was allowed to warm to ambient temperature and stirred overnight; this procedure was repeated. The reaction mixture was diluted with saturated aqueous sodium bicarbonate (~ 100 mL) and dichloromethane (100 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (3 x 50 mL). The combined organics were washed with aqueous sodium bicarbonate (2 x 50 mL), dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide 10.5 g of crude product as a brown solid. This material was triturated with ethyl acetate/hexanes then dried under high vacuum to provide 6.4 g of 7-(4-chlorobutyl)-8-ethoxymethyl-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridine as a white solid.

Part B

Using the general method of Example 26 Part F, 7-(4-chlorobutyl)-8-ethoxymethyl-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridine (7.1 g, 21.1 mmol, 1.0 eq) was reacted with potassium thioacetate (3.61 g, 1.5 eq) to provide 6.5 g of

S-[4-(8-ethoxymethyl-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)butyl] thioacetate as a tan solid.

Part C

Using the general method of Example 26 Part G, S-[4-(8-ethoxymethyl-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)butyl] thioacetate (2.00 g, 5.31 mmol, 1.0 eq) was hydrolyzed to provide 4-(8-ethoxymethyl-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)butane-1-thiol as a yellow solid.

Part D

Using the general method of Example 26 Part H, the material from Part C was oxidized to provide 4-(8-ethoxymethyl-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)butane-1-sulfonyl chloride.

Part E

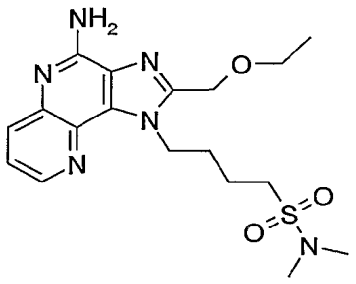
Using the general method of Example 26 Part I, the material from Part D was reacted with dimethylamine hydrochloride. The crude product was purified by HPFC (silica gel eluting with 2-30% CMA in chloroform) to provide 1.1 g of *N,N* dimethyl 4-(8-ethoxymethyl-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)butane-1-sulfonamide.

Part F

Using the general method of Example 26 Part J, *N,N* dimethyl 4-(8-ethoxymethyl-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)butane-1-sulfonamide (0.21 g, 0.51 mmol, 1.0 eq) was reduced. The crude product was triturated with ethyl acetate and dried under high vacuum at 100 °C for 3 hrs to provide 0.11 g of *N,N*-dimethyl 4-(4-amino-6,7-dimethyl-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butane-1-sulfonamide as a white powder, mp 158.0-160.0 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.77 (s, 2H), 4.65 (s, 2H), 4.31 (dd, J = 8.1, 7.1 Hz, 2H), 3.52 (q, J = 7.0 Hz, 2H), 3.08 (dd, J = 7.6, 7.3 Hz, 2H), 2.75 (s, 6H), 2.38 (s, 3H), 2.31 (s, 3H), 1.92-1.68 (m, 4H), 1.15 (t, J = 7.0 Hz, 3H); MS (APCI) *m/z* 384 $(M)^+$; Anal. Calcd for $C_{17}H_{29}N_5O_3S \cdot 0.33H_2O$: C, 52.43; H, 7.68; N, 17.98; Found: C, 52.34; H, 7.81; N, 18.11.

Example 29

N,N-Dimethyl 4-(4-Amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)butane-1-sulfonamide



Part A

Phosphorous oxychloride (38 mL, 1.3 eq) was added dropwise over a period of 70 minutes to a suspension of 4-hydroxy-3-nitro[1,5]naphthyridine (60 g, 314 mmol, 1.0 eq). The orange suspension was stirred at ambient temperature for 5 hrs and then poured into ice water (1.9 L) and stirred for 30 minutes. The solid was isolated by filtration, washed with water (3 x 200 mL), and then dissolved in dichloromethane (1.2 L). The solution was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 61.1 g of 4-chloro-3-nitro[1,5]naphthyridine as an orange solid.

Part B

Triethylamine (6.4 mL, 1.2 eq) was added to a suspension of 4-chloro-3-nitro[1,5]naphthyridine (8.0 g, 38.2 mmol, 1.0 eq) in dichloromethane. The resulting solution was cooled to 5 °C and 4-amino-1-butanol (3.8 mL, 1.1 eq) was added dropwise over a period of 5 minutes. The reaction mixture was allowed to stir at ambient temperature for 3 hrs then it was diluted with saturated aqueous sodium bicarbonate (100 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (2 x 50 mL). The combined organics were dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide 9.94 g of 4-[(3-nitro[1,5]naphthyridin-4-yl)amino]butan-1-ol as a yellow solid.

Part C

Thionyl chloride (3.0 mL, 1.1 eq) was added dropwise to a chilled (0 °C) solution of the material from Part B (1.0 eq) in dichloromethane (190 mL). A white precipitate formed during the addition and additional dichloromethane (170 mL) was added to facilitate stirring. The reaction mixture was allowed to stir at ambient temperature overnight and then it was quenched with 50% saturated sodium bicarbonate (200 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (2 x 75 mL). The combined organics were dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide 10.6 g of *N*-(4-chlorobutyl)-3-nitro[1,5]naphthyridin-4-amine as yellow solid.

Part D

Catalyst (1.1 g of 5% platinum on carbon) was added to a suspension of the material from Part C in ethyl acetate (190 mL). The mixture was placed under hydrogen pressure ((30 psi (2.1×10^5 Pa)) for 2 hours. The reaction mixture was filtered through a layer of CELITE filter aid. The filter cake was rinsed with ethyl acetate (50 mL). The filtrate was concentrated under reduced pressure to provide N^4-(4-chlorobutyl)[1,5]naphthyridine-3,4-diamine as a thick yellow oil.

Part E

Ethoxyacetyl chloride (4.5 mL, 1.1 eq) was added dropwise over a period of 10 minutes to a solution of the material from Part D (1.0 eq) in dichloromethane (180 mL). The reaction mixture was allowed to stir at ambient temperature for 1 hr and then it was concentrated under reduced pressure to provide *N*-[4-(4-chlorobutyl)amino[1,5]naphthyridin-3-yl]-2-ethoxyacetamide hydrochloride.

Part F

The material from Part E was suspended in 3:1 ethanol:water (200 mL). 6M potassium carbonate (9.5 mL, 1.5 eq) was added and the reaction mixture was allowed to stir at ambient temperature for 2 weeks with additional potassium carbonate being added after 1 week. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between dichloromethane (100 mL) and brine (100 mL). The

phases were separated and the aqueous phase was extracted with dichloromethane (50 mL). The combined organics were dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide 12.2 g of 1-(4-chlorobutyl)-2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridine as a brown oil.

Part G

Potassium thioacetate (4.75 g, 1.1 eq) was added in a single portion to a solution of the material from Part F (1.0 eq) in DMF (150 mL). The reaction mixture was stirred overnight and then concentrated under reduced pressure. The residue was dissolved in dichloromethane (200 mL), washed sequentially with water (100 mL) and brine (100 mL), dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide 14.8 g of crude S-[4-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)butyl] thioacetate as a brown oil.

Part H

A portion (1.5 g, 1.0 eq) of the material from Part G was dissolved in methanol (20 mL). The solution was degassed with a nitrogen stream and then sodium methoxide (2.4 mL of 25 wt% in methanol, 2.5 eq) was added dropwise over a period of 3 minutes. The reaction mixture was stirred at ambient temperature for 1 hr and then concentrated under reduced pressure. The residue was partitioned between dichloromethane (70 mL) and water (40 mL). The pH was adjusted to 7 by the addition of 2M hydrochloric acid. The phases were separated and the aqueous phase was extracted with dichloromethane (30 mL). The combined organics were washed with brine (40 mL), dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide 1.36 g of 4-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)butane-1-thiol as a tan solid.

Part I

A solution of sodium chlorate (0.58 g, 1.3 eq) in water (2 mL) was added dropwise over a period of 2 minutes to a chilled (0°C) solution of the material from Part H (1.0 eq) in a mixture of concentrated hydrochloric acid (7 mL) and water (5 mL). The reaction mixture was stirred at 0°C for 1 hr and then diluted with dichloromethane (50 mL). The pH was adjusted to 5 by the addition of 6M potassium carbonate (8 mL) over a period of

20 minutes. The mixture was warmed to ambient temperature and then further diluted with dichloromethane (50 mL) and water (50 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (2 x 20 mL). The combined organics were dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide 1.43 g of 4-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)butane-1-sulfonyl chloride as a pale yellow solid.

Part J

Dimethylamine hydrochloride (0.64 g, 2.1 eq) and 6M potassium carbonate (1.6 mL, 2.5 eq) were added sequentially to a solution of the material from Part I (1.0 eq) in dichloromethane (18 mL). The reaction mixture was stirred at ambient temperature for 1 hr and then diluted with dichloromethane (40 mL) and saturated aqueous sodium bicarbonate (40 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (2 x 20 mL). The combined organics were dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide 1.06 g of an orange solid. This material was purified by HPFC (silica gel eluting with 0-30% CMA in chloroform over 1.2 L) to provide 0.48 g of pure *N,N*-dimethyl 4-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)butane-1-sulfonamide and 0.40 g of a mixture. The mixture was recrystallized from dichloromethane and hexanes to provide an additional 0.27 g of *N,N*-dimethyl 4-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)butane-1-sulfonamide.

Part K

3-Chloroperoxybenzoic acid (0.66 g of 70% , 1.4 eq) was added to a solution of *N,N*-dimethyl 4-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)butane-1-sulfonamide (0.75 g, 1.92 mmol, 1.0 eq) in chloroform (10 mL). The reaction was stirred at ambient temperature for 3 hrs. Analysis by LCMS indicated that the reaction was not complete so additional 3-chloroperoxybenzoic acid (1.4 eq) was added. After an additional 2 hrs of stirring more 3-chloroperoxybenzoic acid (0.42 g) was added and stirring was continued for another hour. The reaction mixture was diluted with saturated aqueous sodium bicarbonate (75 mL) and chloroform (75 mL). The phases were separated and the organic phase was washed with saturated aqueous sodium bicarbonate (75 mL).

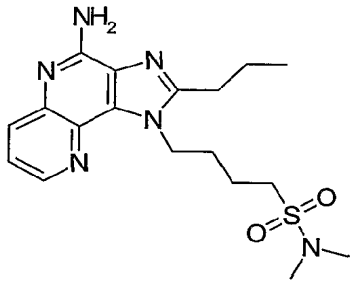
The combined aqueous was extracted with dichloromethane (2 x 30 mL). The combined organics were dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide 1.27 g of *N,N*-dimethyl 4-(2-ethoxymethyl-5-oxy-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)butane-1-sulfonamide as an orange solid.

Part L

Ammonium hydroxide (0.64 mL of 15M, 5.0 eq) was added to a chilled (0 °C) solution of the material from Part K (1.0 eq) in methanol (10 mL). Benzenesulfonyl chloride (0.51 mL, 2.1 eq) was added dropwise. The reaction mixture was stirred at 0°C for 1 hr and then concentrated under reduced pressure. The residue was partitioned between dichloromethane (70 mL) and saturated aqueous sodium bicarbonate (50 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (2 x 20 mL). The combined organics were dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide 1.22 g of crude product as an orange solid. This material was purified twice by HPFC (silica gel eluting with 0-25% CMA in chloroform over 1.3 L, 25 –30% CMA in chloroform over 600 mL; silica gel eluting with 0-30% CMA in chloroform over 960 mL) to provide 0.180 g of a tan solid. This material was recrystallized from chloroform/hexanes and then dried under high vacuum to provide 100 mg of *N,N*-dimethyl 4-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)butane-1-sulfonamide as a white powder, mp 148-150 °C. ^{1}H NMR (300 MHz, DMSO-d6) δ 8.53 (dd, J = 4.4, 1.6 Hz, 1H), 7.92 (dd, J = 8.4, 1.6 Hz, 1H), 7.46 (dd, J = 8.4, 4.4 Hz, 1H), 6.88 (br s, 2H), 4.87 (t, J = 7.4 Hz, 2H), 4.79 (s, 2H), 3.58 (q, J = 7.0 Hz, 2H), 3.09 (t, J = 7.7 Hz, 2H), 2.71 (s, 6H), 2.04 (m, 2H), 1.77 (m, 2H), 1.18 (t, J = 7.0 Hz, 3H); MS (APCI) *m/z* 407 $(M+1)^+$; Anal. calcd for $C_{18}H_{26}N_6O_3S$: C, 53.18; H, 6.45; N, 20.67. Found: C, 52.83; H, 6.40; N, 20.99.

Example 30

N,N-Dimethyl 4-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)butane-1-sulfonamide



Part A

Trimethyl orthobutyrate (7.4 mL, 1.3 eq) and pyridine hydrochloride (0.20 g, 0.05 eq) were added to a solution of N^4-(4-chlorobutyl)[1,5]naphthyridine-3,4-diamine (1.0 eq) in toluene (120 mL). The reaction mixture was heated at reflux for 2 hrs, allowed to cool to ambient temperature, and then concentrated under reduced pressure. The residue was dissolved in dichloromethane (120 mL) and washed with saturated aqueous sodium bicarbonate (100 mL). The aqueous wash was extracted with dichloromethane (2 x 25 mL). The combined organics were dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide 10.8 g of 1-(4-chlorobutyl)-2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridine as a yellow solid.

Part B

Using the general method of Example 29 Part G, 1-(4-chlorobutyl)-2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridine (11.3 g, 37.3 mmol, 1.0 eq) was reacted with potassium thioacetate (4.69 g, 1.1 eq) to provide 15.43 g of crude S-[4-(2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)butyl] thioacetate as a brown oil.

Part C

Using the general method of Example 29 Part H, S-[4-(2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)butyl] thioacetate (3.0 g, 8.76 mmol) was hydrolyzed to provide 2.71 g of 4-(2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)butane-1-thiol as a brown oil.

Part D

Using the general method of Example 29 Part I, the material from Part C was oxidized to provide 2.15 g of 4-(2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)butane-1-sulfonyl chloride as a pale yellow solid.

Part E

Using the general method of Example 29 Part J, the material from Part D (1.0 eq) was reacted with dimethylamine hydrochloride (1.00 g, 2.1 eq) to provide 2.26 g of *N,N*-dimethyl 4-(2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)butane-1-sulfonamide as a yellow solid.

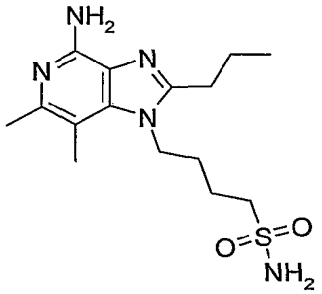
Part F

3-Chloroperoxybenzoic acid (1.98 g of 70%, 1.5 eq) was added to a solution of the material from Part E (1.0 eq) in chloroform (25 mL). The reaction was stirred at ambient temperature for 1 hr. Analysis by LCMS indicated that the reaction was not complete. More 3-chloroperoxybenzoic acid (0.36 g) was added and the reaction mixture was stirred for another hour. Ammonium hydroxide (5 mL) was added followed by the portionwise addition of tosyl chloride (1.12 g, 1.1 eq). The reaction mixture was stirred at ambient temperature for 1 hr and then filtered to remove a white solid. The filtrate was diluted with dichloromethane (50 mL) and saturated aqueous sodium bicarbonate (50 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (2 x 20 mL). The combined organics were dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide 3.03 g of crude product as an orange solid. This material was purified by HPFC (silica gel eluting with 0-30% CMA in chloroform over 1.2 L and 30% CMA in chloroform over 450 mL) to provide 1.36 g of a yellow solid. This material was recrystallized from chloroform/hexanes and then dried under high vacuum at 80 °C for 18 hrs to provide 0.747 g of *N,N*-dimethyl 4-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)butane-1-sulfonamide as an off-white powder, mp 162-163 °C. ^{1}H NMR (300 MHz, DMSO-d6) δ 8.51 (dd, J = 4.3, 1.6 Hz, 1H), 7.91 (dd, J = 8.4, 1.6 Hz, 1H), 7.43 (dd, J = 8.4, 4.3 Hz, 1H), 6.74 (br s, 2H), 4.85 (t, J = 7.2 Hz, 2H), 3.10 (t, J = 7.7 Hz, 2H), 2.92 (t, J = 7.5 Hz, 2H), 2.70 (s, 6H), 1.95 (m, 2H), 1.87 (sextet, J

= 7.5 Hz, 2H), 1.74 (m, 2H), 1.04 (t, J = 7.4 Hz, 3H); MS (APCI) m/z 391 $(M+1)^+$; Anal. calcd for $C_{18}H_{26}N_6O_2S$: C, 55.36; H, 6.71; N, 21.52. Found: C, 55.18; H, 6.98; N, 21.28.

Example 31

4-(4-Amino-6,7-dimethyl-2-propyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butane-1-sulfonamide



Part A

The preparation of 4-(5,6-dimethyl-8-propyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)butane-1-sulfonyl chloride is described in Parts A-H of Example 26. *p*-Methoxybenzylamine (2.37 mL, 18.17 mmol, 2.2 eq) was added dropwise over 3 minutes to a solution of 4-(5,6-dimethyl-8-propyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)butane-1-sulfonyl chloride (3.18 g, 8.26 mmol, 1 eq) in dichloromethane (80 mL) at ambient temperature and stirred overnight. The reaction mixture was diluted with dichloromethane (150 mL) and water (50 mL) and the phases were separated. The aqueous was extracted with dichloromethane (2 x 30 mL). The combined organics were washed sequentially with water (3 mL) and brine (20 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude reaction was purified by HPFC (silica gel eluting with 2-30% CMA in chloroform) to provide 2.01g of *N*-(4-methoxybenzyl) 4-(5,6-dimethyl-8-propyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)butane-1-sulfonamide as a white foam.

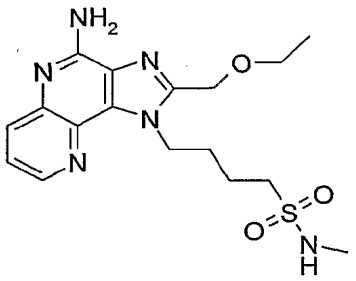
Part B

Platinum IV oxide (340 mg), trifluoroacetic acid (35 mL), and *N*-(4-methoxybenzyl) 4-(5,6-dimethyl-8-propyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)butane-1-sulfonamide (1.7 g, 3.5 mmol) were combined in a pressure vessel and placed under hydrogen pressure (50 psi, 3.4 x 10^5 Pa) until analysis by HPFC indicated the reaction was complete. The reaction mixture was filtered and the filter cake was washed with methanol. The filtrate was concentrated under reduced pressure. The residue was

diluted with 1N hydrochloric acid (~ 10 mL) and then stirred at ambient temperature for 1 hr. The mixture was diluted with chloroform (50 mL) and the pH adjusted to 14 with 6N sodium hydroxide. The phases were separated and the aqueous layer was extracted with chloroform (2 x 30 mL), adjusted to pH of 10 with 1 N hydrochloric acid, and then back extracted with chloroform (4 x 70 mL). The combined organics were dried over sodium sulfate, filtered, concentrated under reduced pressure, triturated with acetonitrile, filtered and dried under high vacuum at 100 °C for 3 hours and 80 °C over night to afford 0.352 g of 4-(4-amino-6,7-dimethyl-2-propyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butane-1-sulfonamide as a white powder, mp 167.0-169.0 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.78 (s, 2H), 5.57 (s, 2H), 4.26-4.18 (m, 2H), 3.08-2.99 (m, 2H), 2.77 (dd, J = 7.7, 7.3 Hz, 2H), 2.37 (s, 3H), 2.30 (s, 3H), 1.86-1.72 (m, 6H), 1.00 (t, J = 7.4 Hz, 3H); MS (APCI) *m/z* 340 $(M)^+$; Anal. Calcd for $C_{15}H_{25}N_5O_2S \cdot 0.2H_2O$ C, 52.52; H, 7.46; N, 20.41; Found: C, 52.59; H, 7.68; N, 20.75.

Example 32

N-Methyl 4-(4-Amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)butane-1-sulfonamide



Part A

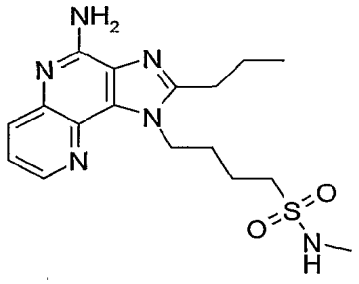
The preparation of 4-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)butane-1-sulfonyl chloride is described in Parts A-I of Example 29. The general method of Part J of Example 29 was repeated using methylamine hydrochloride (0.726 g, 2.1 eq) in lieu of dimethylamine hydrochloride. Recrystallization was unnecessary to provide 1.16 g of *N*-methyl 4-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)butane-1-sulfonamide.

Part B

3-Chloroperoxybenzoic acid (0.96 g of 70%, 2 eq) was added to a solution of *N*-methyl 4-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)butane-1-sulfonamide. (1.05 g, 2.78 mmol, 1 eq) in chloroform (14 mL). The reaction was stirred at ambient temperature for 3 hours followed by sequential addition of ammonium hydroxide (4 mL) and tosyl chloride (0.58 g, 3.06 mmol). The reaction was stirred for 1 hour and additional tosyl chloride (0.20 g) was added. The reaction mixture was diluted with dichloromethane (40 mL) and saturated aqueous sodium bicarbonate. The phases were separated and the aqueous layer was back extracted with dichloromethane (2 x 20 mL). The combined organics were dried over magnesium sulfate, filtered and concentrated under reduced pressure to provide an orange solid. The material was further purified by HPFC (silica gel eluting with 0-30% CMA in chloroform), trituration with acetonitrile, and drying in a vacuum oven at 75 °C to afford 0.503 g of *N*-Methyl 4-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)butane-1-sulfonamide as a white powder, mp 148-150 °C. Anal. calcd for $C_{17}H_{24}N_6O_3S$: C, 52.02; H, 6.16; N, 21.41. Found: C, 51.73; H, 6.41; N, 21.39.

Example 33

N-Methyl 4-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)butane-1-sulfonamide



Part A

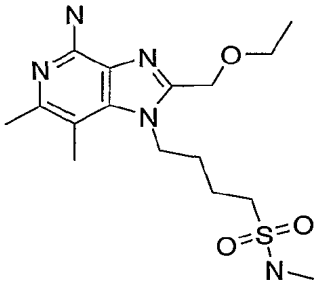
The preparation of 4-(2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)butane-1-sulfonyl chloride is described in Parts A-D of Example 30. The general method of Part J of Example 29 was repeated using methylamine hydrochloride (0.92 g, 2.1 eq) in lieu of dimethylamine hydrochloride to afford 1.64 g of *N*-methyl 4-(2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)butane-1-sulfonamide. Purification by column chromatography or recrystallization was unnecessary for the next reaction.

Part B

3-Chloroperoxybenzoic acid (1.66 g of 70%, 2 eq) was added to a solution of *N*-methyl 4-(2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)butane-1-sulfonamide (1.74 g, 4.81 mmol, 1 eq) in chloroform (25 mL). The reaction was stirred at ambient temperature for 1.5 hours followed by sequential addition of ammonium hydroxide (5 mL) and *p*-toluenesulfonyl chloride (1.01 g, 5.29 mmol). The reaction was stirred for 1 hour and diluted with dichloromethane (40 mL) and saturated aqueous sodium bicarbonate. The phases were separated and the aqueous layer was back extracted with dichloromethane (2 x 20 mL). The combined organics were dried over magnesium sulfate, filtered and concentrated under reduced pressure to provide an orange solid. The material was further purified by HPFC (silica gel eluting with 0-30% CMA in chloroform), trituration with acetonitrile, and drying under high vacuum at 100 °C to afford 0.422 g of *N*-methyl 4-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)butane-1-sulfonamide as an off-white solid, mp 174-175 °C. Anal. calcd for $C_{17}H_{24}N_6O_2S$: C, 54.24; H, 6.43; N, 22.32. Found: C, 54.02; H, 6.42; N, 22.22.

Example 34

N-Methyl 4-(4-Amino-6,7-dimethyl-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl) butane-1-sulfonamide



Part A

Methylamine hydrochloride (0.85 g, 12.5 mmol) was added to a suspension of 4-(8-ethoxymethyl-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)butane-1-sulfonyl chloride (2.38 g, 5.94 mmol, synthesis described in Parts A-D of Example 28) in dichloromethane (60 mL) at ambient temperature. Dropwise addition of 6M potassium carbonate (2.5 mL) followed and the reaction was stirred overnight. The reaction mixture was diluted with dichloromethane (150 mL) and saturated aqueous sodium bicarbonate

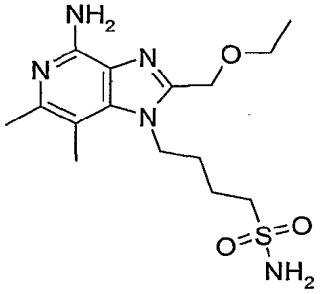
and separated. The aqueous layer was back-extracted with dichloromethane (3 x 50 mL) and the combined organics were washed with saturated aqueous sodium bicarbonate (2 x 50 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford 1.87 g of *N*-methyl 4-(8-ethoxymethyl-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)butane-1-sulfonamide as a white foam.

Part B

Platinum IV oxide (400 mg), trifluoroacetic acid (50 mL), and *N*-methyl 4-(8-ethoxymethyl-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)butane-1-sulfonamide (1.87 g, 4.73 mmol) were combined in a pressure vessel and placed under hydrogen pressure (50 psi, 3.4 x 10^5 Pa) and agitated over the weekend. Analysis by HPLC indicated the reaction was incomplete and additional platinum IV oxide (150 mg) was added. After 24 hours, the reaction mixture was filtered and the filter cake was washed with methanol. The filtrate was concentrated under reduced pressure. The residue was diluted with 1N hydrochloric acid (~5 mL) and then stirred at ambient temperature for 1 hr. The mixture was cooled to 0 °C and diluted with chloroform (100 mL) and the pH adjusted to 14 with 6N sodium hydroxide. The phases were separated and the aqueous layer was extracted with chloroform (3 x 100 mL). The combined organics were dried over sodium sulfate, filtered, and concentrated under reduced pressure, triturated with acetonitrile, filtered and concentrated to give a white solid. The material was further purified by HPFC (silica gel eluting with 15-40% CMA in chloroform) and recrystallized from acetonitrile to afford 0.592 g of *N*-methyl 4-(4-amino-6,7-dimethyl-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butane-1-sulfonamide as a white powder, mp 194.5-196.0 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.89 (q, J = 5.0 Hz, 1H), 5.77 (s, 2H), 4.65 (s, 2H), 4.30 (dd, J = 8.2, 7.3 Hz, 2H), 3.51 (q, J = 7.0 Hz, 2H), 3.05 (dd, J = 7.7, 7.3 Hz, 2H), 2.56 (d, J = 5.0 Hz, 3H), 2.38 (s, 3H), 2.31 (s, 3H), 1.92-1.66 (m, 4H), 1.15 (t, J = 7.0 Hz, 3H); MS (APCI) *m/z* 370 $(M)^+$; Anal. Calcd for $C_{16}H_{27}N_5O_3S$ C, 52.01; H, 7.37; N, 18.95; Found: C, 51.92; H, 7.45; N, 19.04.

Example 35

4-(4-Amino-2-ethoxymethyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butane-1-sulfonamide



Part A

The general method of Example 31 was followed using 4-(8-ethoxymethyl-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)butane-1-sulfonyl chloride (2.38 g, 5.94 mmol, synthesis described in Parts A-D of Example 28) in lieu of 4-(5,6-dimethyl-8-propyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)butane-1-sulfonyl chloride. Purification was performed by successive triturations with ethyl acetate in lieu of column chromatography to afford 1.73 g of *N*-(4-methoxybenzyl) 4-(8-ethoxymethyl-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)butane-1-sulfonamide.

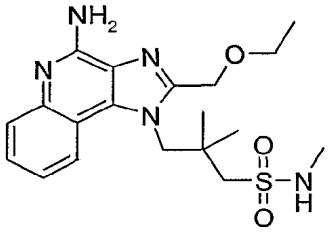
Part B

Platinum IV oxide (350 mg), trifluoroacetic acid (35 mL), and *N*-(4-methoxybenzyl) 4-(8-ethoxymethyl-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)butane-1-sulfonamide (1.73 g, 3.45 mmol) were combined in a pressure vessel and placed under hydrogen pressure (50 psi, 3.4 x 10^5 Pa) until analysis by HPLC indicated the reaction was complete. The reaction mixture was filtered and the filter cake was washed with methanol. The filtrate was concentrated under reduced pressure. The residue was diluted with 1N hydrochloric acid (~ 10 mL) and then stirred at ambient temperature for 1 hr. The mixture was cooled to 0 °C and diluted with chloroform (100 mL) and the pH adjusted to 14 with 6N sodium hydroxide. The phases were separated and the aqueous layer was adjusted to pH 7 with 1N hydrochloric acid and back-extracted with chloroform (2 x 30 mL). The combined organics were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The solids were triturated sequentially with acetonitrile and ethyl acetate and dried under high vacuum at 80 °C. Under sonication for

3 minutes, 6N sodium hydroxide (5 mL) and water (3 mL) were added to the solid, followed by adjustment of the pH of the mixture to 11 with 6N hydrochloric acid. The solution was cooled to 0 °C, filtered, washed with water, triturated with acetonitrile to afford 237 mg of 4-(4-amino-2-ethoxymethyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butane-1-sulfonamide as a white powder, mp 200.0-201.5 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.79 (s, 2H), 5.77 (s, 2H), 4.66 (s, 2H), 4.30 (dd, J = 8.0, 6.4 Hz, 2H), 3.51 (q, J = 7.0 Hz, 2H), 3.03 (dd, J = 7.7, 6.6 Hz, 2H), 2.38 (s, 3H), 2.31 (s, 3H), 1.91-1.71 (m, 4H), 1.15 (t, J = 7.0 Hz, 3H); MS (APCI) *m/z* 356 $(M)^+$; Anal. Calcd for $C_{15}H_{25}N_5O_3S \cdot 0.4H_2O$ C, 49.68; H, 7.17; N, 19.31; Found: C, 49.97; H, 7.38; N, 19.67.

Example 36

3-[4-Amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-*N*,2,2-trimethylpropane-1-sulfonamide



Part A

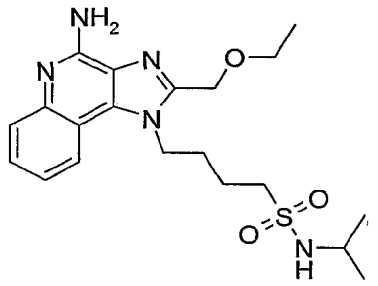
Using the general method of Example 11 Part A, 3-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2,2-dimethylpropane-1-sulfonyl chloride (2.33 g, 5.88 mmol, 1.0 eq) was reacted with methylamine hydrochloride (834 mg, 2.1 eq) to provide 2.0 g of crude product. This material was purified by HPFC (silica gel eluting with 0-100% B in chloroform over 8 column volumes and then 100% B for 7 column volumes, B is premixed 5:95 methanol:chloroform) to provide 1.5 g of an off white foam. This material was purified by HPFC (silica gel eluting with 0-10% B in ethyl acetate for 6 column volumes and then 10% B for 6 column volumes, B is 10% methanol in ethyl acetate) to provide 0.90 g of 3-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-*N*,2,2-trimethylpropane-1-sulfonamide as a white foam.

Part B

Using the general method of Example 11 Part B, the material from Part A was oxidized and then aminated. The crude product was triturated sequentially with ethyl acetate and acetonitrile to provide 270 mg of 3-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-*N*,2,2-trimethylpropane-1-sulfonamide as a tan powder, mp 161-163 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.38 (d, J=7.7 Hz, 1H), 7.59 (dd, J=1.2, 8.3 Hz, 1H), 7.42 (m, 1H), 7.21 (m, 1H), 7.02 (q, J=5.0 Hz, 1H), 6.61 (br s, 2H), 5.04-4.70 (m, 4H), 3.55 (br, 2H), 2.61 (dd, J=4.9 Hz, 3H), 1.14 (t, J=7.0 Hz, 3H), 1.03 (br s, 6H); MS (APCI) *m/z* 406 $(M+H)^+$; Anal. calcd for $C_{19}H_{27}N_5O_3S$: C, 56.28; H, 6.71; N, 17.27. Found: C, 56.24; H, 6.69; N, 17.06.

Example 37

4-[4-Amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-*N*-isopropylbutane-1-sulfonamide



Part A

Using the general method of Example 11 Part A, 3-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butane-1-sulfonyl chloride (4.1 g, 10.7 mmol, 1.0 eq) was reacted with isopropyl amine (0.70 g, 11.8 mmol, 1.1 eq) to provide 4.2 g of crude product. This material was purified by HPFC (silica gel eluting with 17% CMA in chloroform for 7 column volumes) to provide 2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-*N*-isopropylbutane-1-sulfonamide.

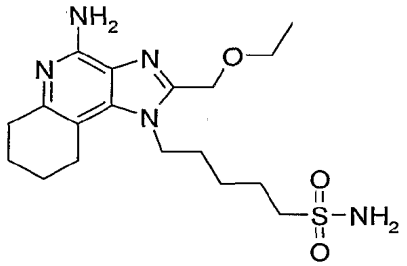
Part B

Using the general method of Example 11 Part B, the material from Part A was oxidized and then aminated. The crude product was purified by trituration with acetonitrile followed by recrystallization from ethanol to provide 176 mg of product. The

filtrate was concentrated and the residue was purified by HPFC (silica gel eluting with 0-20% CMA in chloroform over 8 column volumes and then with 20% CMA in chloroform for 9 column volumes) to provide 0.36 g of a light yellow oil. This material was triturated with ethanol (15 mL). The resulting solid was isolated by filtration, rinsed with ethanol (2 x 2 mL), and then dried under high vacuum at 80 °C to provide 214 mg of 4-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-*N*-isopropylbutane-1-sulfonamide as a white powder, mp 146-147°C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.05 (d, J=7.6 Hz, 1H), 7.62 (dd, J=1.1, 8.3 Hz, 1H), 7.45 (m, 1H), 7.26 (m, 1H), 6.99 (d, J=7.6 Hz, 1H), 6.58 (br s, 2H), 4.78 (s, 2H), 4.60 (m, 2H), 3.57 (q, J=7.0 Hz, 2H), 3.38 (m, 1H), 3.05 (m, 2H), 1.98 (m, 2H), 1.84 (m, 2H), 1.17 (t, J=7.0 Hz, 3H), 1.09 (d, J=6.5 Hz, 6H); MS (APCI) *m/z* 420 $(M+H)^+$; Anal. calcd for $C_{20}H_{29}N_5O_3S$: C, 57.26; H, 6.97; N, 16.69. Found: C, 57.15; H, 6.96; N, 16.77.

Example 38

5-[4-amino-2-(ethoxymethyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl]pentane-1-sulfonamide

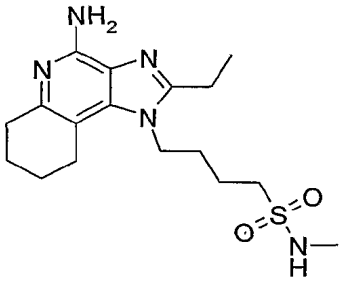


5-[4-Amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]pentane-1-sulfonamide (1.2 g) was reduced using the general method of Example 18. The crude product was placed under high vacuum until the clear oil had a steady weight of 1.2 g. The oil was combined with water (10 mL) and the pH was adjusted to pH 12 with 10% sodium hydroxide. The mixture was stirred for an hour and then filtered. The filtrate was adjusted to pH 7.5 with 6M hydrochloric acid. The resulting precipitate was isolated by filtration, recrystallized from methanol and then dried to provide a white solid. This material was dissolved in 12M hydrochloric acid (5 mL) and then stirred overnight. The mixture was chilled in an ice bath and then the pH was adjusted to pH 8 by slowly adding 6M potassium carbonate. The resulting suspension was stirred for 2 hours and the pH was

adjusted to pH 12 with 10% sodium hydroxide. After stirring for an additional 2 hours the mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was recrystallized from methanol and then dried under vacuum at 78 °C overnight to provide about 0.17 g of a white solid. This material was slurried with hot water and then allowed to cool to ambient temperature. The solid was isolated by filtration, rinsed with water (2 x 1 mL), air dried, and then dried under high vacuum at 110 °C for 15 minutes to provide 178 mg of 5-[4-amino-2-(ethoxymethyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl]pentane-1-sulfonamide as a white powder, mp 203-205°C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.73 (s, 2H), 5.80 (s, 2H), 4.64 (s, 2H), 4.24 (m, 2H), 3.50 (q, J=7.0 Hz, 2H), 2.98 (m, 4H), 2.66 (m, 2H), 1.77 (m, 8H), 1.47 (m, 2H), 1.14 (t, J=7.0 Hz, 3H); MS (APCI) *m/z* 396 $(M+H)^+$; Anal. calcd for $C_{18}H_{29}N_5O_3S$: C, 54.66; H, 7.39; N, 17.71. Found: C, 54.59; H, 7.65; N, 17.88.

Example 39

N-Methyl 4-(4-amino-2-ethyl-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide

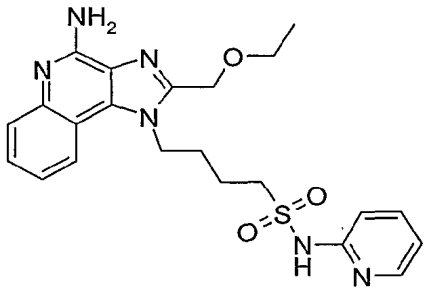


N-Methyl 4-(4-amino-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide (420 mg) was reduced using the general method of Example 18. The reaction mixture was diluted with chloroform (5 mL) and methanol (10 mL) and then filtered through a layer of CELITE filter aid. The filter cake was rinsed with methanol (2 x 2 mL). The filtrate was concentrated under reduced pressure. The residue was combined with dichloromethane (50 mL) and saturated aqueous sodium bicarbonate (about 20 mL) and the mixture was stirred vigorously for 30 minutes. The organic layer was separated, dried over magnesium sulfate, and then concentrated under reduced pressure to provide 0.51 g of crude product as a white solid. A 50 mg portion was removed. The remaining material

was combined with concentrated hydrochloric acid (about 10 mL) to provide a hazy solution. 6M potassium carbonate was added dropwise with cooling to maintain the temperature below 35 – 40 °C until the pH was about 10 – 11. The mixture was stirred for about 10 minutes. The resulting precipitate was isolated by filtration, rinsed with water (3 x 4 mL), and dried under high vacuum to provide 338 mg of a white solid. This material was purified by HPFC (silica gel eluting for 15 column volumes with 10/90 methanol/chloroform) to provide a clear oil. The oil was transferred to a vial with dichloromethane; partial evaporation of the solvent provided a white solid. This material was isolated by filtration, rinsed with dichloromethane (2 x 1 mL), and dried under high vacuum to provide 202 mg of a white crystalline solid. This material was dissolved in warm methanol (about 9 mL), concentrated under reduced pressure, and then dried under high vacuum to provide a clear oil. The oil was dissolved in 1/1 methanol/ethyl acetate (about 8 mL), concentrated under reduced pressure, and then dried under high vacuum at 75 °C to provide 138 mg of *N*-methyl 4-(4-amino-2-ethyl-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide as a white powder, mp 166-170 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.88 (q, J=5.0 Hz, 1H), 5.81 (br s, 2H), 4.20 (m, 2H), 3.06 (m, 2H), 2.94 (m, 2H), 2.82 (q, J=7.5 Hz, 2H), 2.66 (m, 2H), 2.56 (d, J=5.0 Hz, 3H), 1.76 (m, 8H), 1.32 (t, J=7.4 Hz, 3H); MS (APCI) *m/z* 366 $(M+H)^+$; Anal. calcd for $C_{17}H_{27}N_5O_2S \cdot 0.50\ H_2O$: C, 54.52; H, 7.54; N, 18.70. Found: C, 54.82; H, 7.71; N, 18.58.

Example 40

4-[4-Amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-*N*-(pyridin-2-yl)butane-1-sulfonamide



Part A

Using the general method of Example 8 Part I, 1-(4-chlorobutyl)-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline (21.2 g) was oxidized and then aminated to provide 26.8 g of crude product as a brown solid. This material was triturated with ethyl acetate (100 mL). The resulting off white solid was isolated by filtration, rinsed with ethyl acetate (3 x 30 mL), and dried under high vacuum to provide 15.18 g of 1-(4-chlorobutyl)-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine.

Part B

Using the general method of Example 8 Part E, 1-(4-chlorobutyl)-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (2.00 g, 6.02 mmol) was reacted with potassium thioacetate (824 mg, 7.23 mmol) to provide 2.23 g of S-[4-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl] thioacetate as yellow powder.

Part C

The material from Part B was hydrolyzed using the general method of Example 8 Part F. The crude product was purified by flash chromatography (5 x 15 cm column of silica gel eluting with a gradient of 10 to 20 % CMA in chloroform) to provide 1.43 g of 4-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-thiol.

Part D

Using the general method of Example 8 Part G, 4-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-thiol (380 mg) was oxidized to provide 280 mg of 4-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonyl chloride as a brown foam.

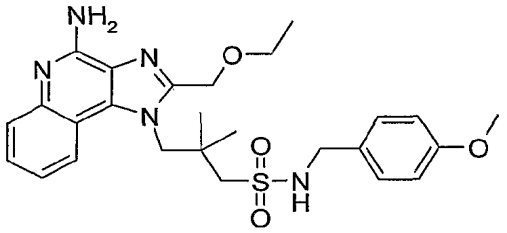
Part E

Solid 2-aminopyridine (265 mg, 4 eq) was added to the material from Part D (1 eq) followed by the rapid addition of pyridine (3.5 mL). The resulting solution was stirred at ambient temperature for 1 hr and then concentrated under reduced pressure. The residue was diluted with methanol (40 mL), concentrated under reduced pressure, and then dried under high vacuum. The residue was suspended in warm 1/1 methanol/dichloromethane,

absorbed onto silica gel, and then purified by HPFC (eluting with a gradient of 0 to 35 % CMA in chloroform over 15 column volumes and then with 35 % CMA in chloroform for 8 column volumes) to provide 79 mg of a light yellow solid. This material was recrystallized from ethanol and then dried under high vacuum at 75 – 100 °C until analysis by ^{1}H NMR indicated that the ethanol had been removed to provide 62 mg of 4-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-*N*-(pyridin-2-yl)butane-1-sulfonamide as light yellow powder, mp 197-200 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ10.89 (br s, 1H), 8.15 (d, J=5.4 Hz, 1H), 8.04 (d, J=7.8 Hz, 1H), 7.71 (ddd, J=1.9, 7.3, 8.5 Hz, 1H), 7.62 (dd, J=1.1, 8.3 Hz, 1H), 7.45 (m, 1H), 7.25 (m, 1H), 6.99 (m, 2H), 6.63 (br s, 2H), 4.76 (s, 2H), 4.59 (m, 2H), 3.51 (m, 4H), 1.94 (m, 4H), 1.11 (t, J=7.0 Hz, 3H); MS (APCI) *m/z* 455 $(M+H)^+$; Anal. calcd for $C_{22}H_{26}N_6O_3S$: C, 58.13; H, 5.77; N, 18.49. Found: C, 57.95; H, 5.71; N, 18.28.

Example 41

3-[4-Amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-*N*-(4-methoxybenzyl)-2,2-dimethylpropane-1-sulfonamide



Part A

4-Methoxybenzylamine (1.96 mL, 2.1 eq) was added to a solution of 3-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropane-1-sulfonyl chloride (2.83 g, 1.0 eq) in dichloromethane (36 mL). The resulting suspension was stirred for 1 hour at ambient temperature then diluted with dichloromethane (100 mL) and washed with water (40 mL). The organic layer was dried over magnesium sulfate and concentrated under reduced pressure to provide 3.3 g of crude product as an oil. This material was purified by HPFC (silica gel eluting with 0-20% CMA in chloroform for 8 column volumes and then 20% CMA in chloroform for 3 column volumes) to provide 1.63 g of 3-

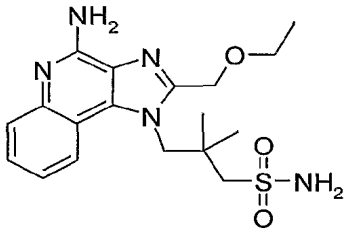
[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-*N*-(4-methoxybenzyl)-2,2-dimethylpropane-1-sulfonamide as a light yellow foam.

Part B

Using the general method of Example 8 Part I, the material from Part A was oxidized and then aminated to provide 1.87 g of crude product as a tan foam. This material was purified by HPFC (silica gel eluting with 0-20% CMA in chloroform for 7 column volumes and then 20% CMA in chloroform for 5 column volumes) to provide 1.36 g of a tan foam. This material was triturated with methanol (10 mL), isolated by filtration, rinsed with methanol (3 x 7 mL), and then dried under high vacuum to provide 993 mg of 3-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-*N*-(4-methoxybenzyl)-2,2-dimethylpropane-1-sulfonamide as a white powder, mp 203-205 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.36 (d, J=8.5 Hz, 1H), 7.61 (m, 2H), 7.42 (m, 1H), 7.23 (m, 3H), 6.92 (m, 2H), 6.61 (br s, 2H), 4.68 (br m, 4H), 4.09 (d, J=6.0 Hz, 2H), 3.75 (s, 3H), 3.55 (br, 2H), 1.14 (t, J=7.0 Hz, 3H), 1.03 (s, 6H); MS (APCI) *m/z* 512 $(M+H)^+$; Anal. calcd for $C_{26}H_{33}N_5O_4S$: C, 61.04; H, 6.50; N, 13.69. Found: C, 60.87; H, 6.60; N, 13.68.

Example 42

3-[4-Amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2,2-dimethylpropane-1-sulfonamide

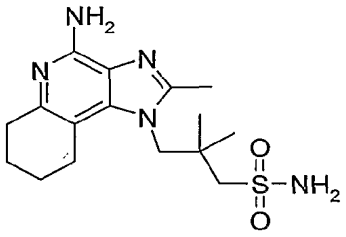


Trifluoroacetic acid (8 mL) and anisole (213 μL, 1.2 eq) were added sequentially to solid 3-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-*N*-(4-methoxybenzyl)-2,2-dimethylpropane-1-sulfonamide (834 mg, 1.63 mmol, 1.0 eq). The resulting solution was stirred at ambient temperature for 22 hours and then concentrated under reduced pressure. The residue was partitioned between dichloromethane (50 mL) and saturated aqueous sodium bicarbonate (about 35 mL). The layers were separated and

the aqueous layer was extracted with chloroform (1 x 40 mL) and then with 10 % methanol in chloroform (4 x 25 mL). The combined organics were dried over magnesium sulfate and then concentrated under reduced pressure to provide 1.15 g of a light yellow semisolid. This material was dissolved in 10 % methanol in ethyl acetate, allowed to stand for 1 hour, and then filtered to remove a small amount of insoluble material which had formed on standing. The filtrate was concentrated under reduced pressure and then dried under high vacuum. The residue was triturated with methanol (about 5 mL), isolated by filtration, and rinsed with methanol (4 x 2 mL) to provide 475 mg of a yellow solid. This material was slurried with hot 5 % methanol in chloroform (about 3 – 4 mL), allowed to cool to ambient temperature, isolated by filtration, rinsed with 5 % methanol in chloroform (3 x 1 mL), and then dried under high vacuum to provide 395 mg of a light yellow solid. This process was repeated to provide 352 mg of 3-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2,2-dimethylpropane-1-sulfonamide as light yellow powder, mp 229-231 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ8.36 (d, J=8.0 Hz, 1H), 7.59 (dd, J=1.1, 8.3 Hz, 1H), 7.42 (m, 1H), 7.21 (m, 1H), 7.02 (br s, 2H), 6.61 (br s, 2H), 4.70 (m, 4H), 3.55 (br, 2H), 1.14 (t, J=7.0 Hz, 3H), 1.05 (s, 6H); MS (EI) *m/z* 392 $(M+H)^+$; Anal. calcd for $C_{18}H_{25}N_5O_3S$: C, 55.22; H, 6.44; N, 17.89. Found: C, 55.02; H, 6.64; N, 18.08.

Example 43

3-(4-Amino-2-methyl-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropane-1-sulfonamide



Part A

Tosyl chloride (4.67 g, 1.2 eq.) and 4-dimethylaminopyridine (46 mg, 0.02 eq) were added sequentially to a suspension of 2,2-dimethyl-3-[(3-nitroquinolin-4-yl)amino]propanol (5.19 g, 18.8 mmol, 1.0 eq) in pyridine (35 mL). The reaction mixture was stirred at ambient temperature over night and then concentrated under reduced pressure. The residue was dilute with chloroform (300 mL) and washed with water (60

mL). The aqueous wash was extracted with dichloromethane (75 mL). The combined organics were dried over magnesium sulfate and then concentrated under reduced pressure to provide 7.88 g of 2,2-dimethyl-3-[(3-nitroquinolin-4-yl)amino]propyl *p*-toluenesulfonate as a yellow solid.

Part B

A mixture of 2,2-dimethyl-3-[(3-nitroquinolin-4-yl)amino]propyl *p*-toluenesulfonate (5.37 g, 12.5 mmol), 10 % palladium on carbon (530 mg), and acetonitrile was placed under hydrogen pressure (50 psi, 3.4 x 10^5 Pa) on a Parr apparatus for 6 hours. The reaction mixture was filtered through a layer of CELITE filter aid. The filter cake was rinsed with acetonitrile until the rinse was colorless. The filtrate was concentrated under reduced pressure to provide 4.50 g of crude 3-[(3-aminoquinolin-4-yl)amino]-2,2-dimethylpropyl *p*-toluenesulfonate as an orange oil.

Part C

Trimethyl orthoacetate (1.72 mL, 1.2 eq) and pyridine hydrochloride (130 mg, 0.1 eq) were added sequentially to a suspension of the material from Part B (1 eq) in toluene (111 mL). The reaction mixture was heated at 100 °C for 1 hour, cooled to ambient temperature overnight, combined with the material from another run, and then concentrated under reduced pressure to provide 5.50 g of crude product as a brown foam. This material was purified by HPFC (silica gel eluting with a gradient of 0 to 20 % CMA in chloroform over 7 column volumes and then with 20% CMA in chloroform for 5 column volumes) to provide 3.94 g of 3-(2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropyl *p*-toluenesulfonate as a white foam.

Part D

Potassium thiocyanate (155 mg, 2.0 eq) was added to a solution of 3-(2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropyl *p*-toluenesulfonate (338 mg, 0.80 mmol, 1.0 eq) in *n*-propanol (4.0 mL). The reaction mixture was heated in an EMRYS OPTIMIZER microwave synthesizer (available from Biotage, Inc, Charlottesville, Virginia, USA) at 190 °C for 20 minutes. The reaction was repeated. The combined reaction mixtures were concentrated under reduced pressure. The residue was partitioned

between chloroform (100 mL) and water (75 mL). The organic layer was washed with brine (50 mL), dried over magnesium sulfate, and concentrated under reduced pressure to provide 0.50 g of an oil. The oil was purified by HPFC (silica gel eluting with a gradient of 0 to 20 % CMA in chloroform over 8 column volumes and then with 20% CMA in chloroform for 4 column volumes) to provide 390 mg of 3-(2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropyl thiocyanate as a clear oil.

Part E

Sodium borohydride (95 mg, 2.0 eq) was added to a chilled (0 °C) solution of the material from Part D (1.0 eq) in ethanol (12 mL). The reaction mixture was allowed to warm to ambient temperature. After 3 hours the reaction was quenched with hydrochloric acid (about 1 mL of 7 M), stirred for several minutes, and then concentrated under reduced pressure. The residue was dissolved in dichloromethane (125 mL) then water (75 mL) was added. The mixture was made basic (pH about 7) with saturated sodium bicarbonate. The organic layer was separated, dried over magnesium sulfate, and concentrated under reduced pressure to provide 330 mg of 3-(2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropane-1-thiol as an oil.

Part F

A solution of benzyltrimethylammonium chloride (663 mg, 3.4 eq) and trichloroisocyanuric acid (268 mg, 1.1 eq) in dichloromethane (5 mL) was stirred at ambient temperature for 45 minutes and then added dropwise over a period of about 2 minutes to a chilled (0 °C) solution of the material from Part E (1.0 eq) and water (47 μL, 2.5 eq) in dichloromethane (6 mL). After 45 minutes 4-methoxybenzylamine (0.89 mL, 6.5 eq) was added and then the reaction mixture was allowed to warm to ambient temperature and stirred for 2 hours. The reaction mixture was diluted with dichloromethane (125 mL), washed with water (2 x 200 mL), dried over magnesium sulfate, and then concentrated under reduced pressure to provide 0.67 g of crude product as an oil. The oil was purified by HPFC (silica gel eluting with a gradient of 0 to 20 % CMA in chloroform over 8 column volumes and then with 20% CMA in chloroform for 4 column volumes) and combined with the material from another run to provide 757 mg of

N-(4-methxoybenzyl) 3-(2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropane-1-sulfonamide as a white foam.

Part G

3-Chloroperoxybenzoic acid (490 mg, 1.2 eq based on a 70% titer) was added to a solution of the material from Part F (1.0 eq) in chloroform (16 mL). The reaction mixture was stirred at ambient temperature for 40 minutes and then combined with concentrated ammonium hydroxide (4 mL). Tosyl chloride (379 mg, 1.2 eq) was added in portions over a period of several minutes. The reaction mixture was stirred for 1 hour and then diluted with chloroform (100 mL) and washed with water (50 mL). The aqueous layer was extracted with dichloromethane (30 mL). The combined organics were dried over magnesium sulfate and concentrated under reduced pressure to provide 0.89 g of crude product as a brown foam. This material was purified by HPFC (silica gel eluting with a gradient of 0 to 30 % CMA in chloroform over 8 column volumes and then with 30% CMA in chloroform for 8 column volumes) to provide 500 mg of 3-(4-amino-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-(4-methxoybenzyl)-2,2-dimethylpropane-1-sulfonamide as a tan/orange powder.

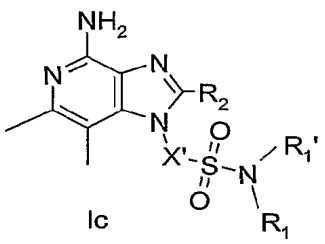
Part H

The material from Part G was dissolved in trifluoroacetic acid (11 mL) and stirred at ambient temperature for 4.5 hours. Platinum (IV) oxide (500 mg) was added and the mixture was placed under hydrogen pressure (50 psi, 3.4 x 10^5 Pa) on a Parr apparatus for 20 hours. The reaction mixture was filtered through a layer of CELITE filter aid. The filter cake was rinsed sequentially with trifluoroacetic acid (2 x 8 mL), methanol (3 x 15 mL), and 1/1 methanol/chloroform (2 x 15 mL). The filtrate was concentrated under reduced pressure. The residue was partitioned between dichloromethane (150 mL) and water (75 mL) and the aqueous pH was adjusted to about 8 - 9. The layers were separated. The aqueous layer was extracted with dichloromethane (3 x 50 mL) and 10% methanol in dichloromethane (2 x 50 mL). The combined organics were dried over magnesium sulfate and concentrated under reduced pressure to provide 0.44 g of crude product as a brown semisolid. This material was purified by HPFC (silica gel eluting with a gradient of 20 to 50 % CMA in chloroform over 5 column volumes and then with 50% CMA in chloroform

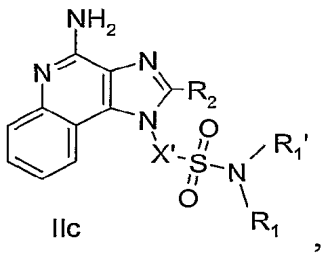
for 6 column volumes) to provide 180 mg of a white semisolid. This material was crystallized from hot isopropanol (about 8 mL), isolated by filtration, rinsed with isopropanol (3 x 2 mL), and dried under high vacuum to provide 131 mg of a white solid. This material was dissolved in hot methanol, the methanol solution was concentrated, and the solid was isolated by filtration. This procedure was repeated using ethanol and the resulting solid was dried under high vacuum at 100 °C for 48 hours to provide about 125 mg of 3-(4-amino-2-methyl-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropane-1-sulfonamide as an off white solid, mp 242-243 °C (dec.). ^{1}H NMR (300 MHz, DMSO-d_6): δ6.97 (s, 2H), 5.71 (s, 2H), 4.38 (br, 2H), 3.15 (br, 2H), 2.88 (br, 2H), 2.66 (br, 2H), 1.74 (br, 4H), 1.01 (s, 6H); MS (EI) *m/z* 352 $(M+H)^+$; Anal. calcd for $C_{16}H_{25}N_5O_2S \cdot 0.10\ C_3H_8O \cdot 0.22\ H_2O$: C, 54.17; H, 7.32; N, 19.38. Found: C, 54.01; H, 7.16; N, 19.44.

Exemplary Compounds

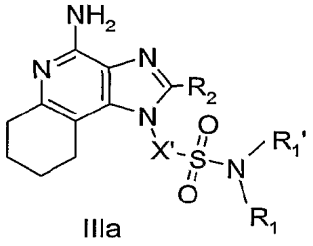
Certain exemplary compounds, including some of those described above in the Examples, have the following Formulas Ic, IIc, IIIa, and IVa and the following R_1, R_1', X', and R_2 substituents, wherein each line of the table represents a specific compound.



Ic

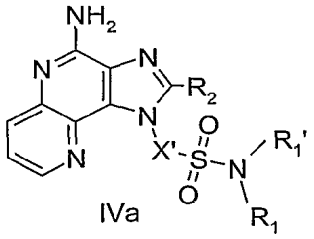


IIc



IIIa

and



IVa

R_1	R_1'	X'	R_2
hydrogen	hydrogen	$-(CH_2)_2-$	methyl
hydrogen	hydrogen	$-(CH_2)_2-$	ethyl
hydrogen	hydrogen	$-(CH_2)_2-$	n-propyl
hydrogen	hydrogen	$-(CH_2)_2-$	n-butyl
hydrogen	hydrogen	$-(CH_2)_2-$	ethoxymethyl
hydrogen	hydrogen	$-(CH_2)_2-$	2-methoxyethyl
hydrogen	hydrogen	$-(CH_2)_2-$	hydroxymethyl
hydrogen	hydrogen	$-(CH_2)_2-$	2-hydroxyethyl
hydrogen	hydrogen	$-(CH_2)_3-$	methyl
hydrogen	hydrogen	$-(CH_2)_3-$	ethyl
hydrogen	hydrogen	$-(CH_2)_3-$	n-propyl
hydrogen	hydrogen	$-(CH_2)_3-$	n-butyl
hydrogen	hydrogen	$-(CH_2)_3-$	ethoxymethyl
hydrogen	hydrogen	$-(CH_2)_3-$	2-methoxyethyl
hydrogen	hydrogen	$-(CH_2)_3-$	hydroxymethyl
hydrogen	hydrogen	$-(CH_2)_3-$	2-hydroxyethyl
hydrogen	hydrogen	$-(CH_2)_4-$	methyl
hydrogen	hydrogen	$-(CH_2)_4-$	ethyl
hydrogen	hydrogen	$-(CH_2)_4-$	n-propyl
hydrogen	hydrogen	$-(CH_2)_4-$	n-butyl
hydrogen	hydrogen	$-(CH_2)_4-$	ethoxymethyl
hydrogen	hydrogen	$-(CH_2)_4-$	2-methoxyethyl
hydrogen	hydrogen	$-(CH_2)_4-$	hydroxymethyl
hydrogen	hydrogen	$-(CH_2)_4-$	2-hydroxyethyl
hydrogen	hydrogen	$-(CH_2)_5-$	methyl
hydrogen	hydrogen	$-(CH_2)_5-$	ethyl
hydrogen	hydrogen	$-(CH_2)_5-$	n-propyl
hydrogen	hydrogen	$-(CH_2)_5-$	n-butyl
hydrogen	hydrogen	$-(CH_2)_5-$	ethoxymethyl
hydrogen	hydrogen	$-(CH_2)_5-$	2-methoxyethyl
hydrogen	hydrogen	$-(CH_2)_5-$	hydroxymethyl
hydrogen	hydrogen	$-(CH_2)_5-$	2-hydroxyethyl
hydrogen	hydrogen	$-CH_2C(CH_3)_2CH_2-$	methyl
hydrogen	hydrogen	$-CH_2C(CH_3)_2CH_2-$	ethyl
hydrogen	hydrogen	$-CH_2C(CH_3)_2CH_2-$	n-propyl
hydrogen	hydrogen	$-CH_2C(CH_3)_2CH_2-$	n-butyl
hydrogen	hydrogen	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
hydrogen	hydrogen	$-CH_2C(CH_3)_2CH_2-$	2-methoxyethyl
hydrogen	hydrogen	$-CH_2C(CH_3)_2CH_2-$	hydroxymethyl
hydrogen	hydrogen	$-CH_2C(CH_3)_2CH_2-$	2-hydroxyethyl
isopropyl	hydrogen	$-(CH_2)_2-$	methyl
isopropyl	hydrogen	$-(CH_2)_2-$	ethyl
isopropyl	hydrogen	$-(CH_2)_2-$	n-propyl
isopropyl	hydrogen	$-(CH_2)_2-$	n-butyl

R_1	R_1'	X'	R_2
isopropyl	hydrogen	$-(CH_2)_2-$	ethoxymethyl
isopropyl	hydrogen	$-(CH_2)_2-$	2-methoxyethyl
isopropyl	hydrogen	$-(CH_2)_2-$	hydroxymethyl
isopropyl	hydrogen	$-(CH_2)_2-$	2-hydroxyethyl
isopropyl	hydrogen	$-(CH_2)_3-$	methyl
isopropyl	hydrogen	$-(CH_2)_3-$	ethyl
isopropyl	hydrogen	$-(CH_2)_3-$	n-propyl
isopropyl	hydrogen	$-(CH_2)_3-$	n-butyl
isopropyl	hydrogen	$-(CH_2)_3-$	ethoxymethyl
isopropyl	hydrogen	$-(CH_2)_3-$	2-methoxyethyl
isopropyl	hydrogen	$-(CH_2)_3-$	hydroxymethyl
isopropyl	hydrogen	$-(CH_2)_3-$	2-hydroxyethyl
isopropyl	hydrogen	$-(CH_2)_4-$	methyl
isopropyl	hydrogen	$-(CH_2)_4-$	ethyl
isopropyl	hydrogen	$-(CH_2)_4-$	n-propyl
isopropyl	hydrogen	$-(CH_2)_4-$	n-butyl
isopropyl	hydrogen	$-(CH_2)_4-$	ethoxymethyl
isopropyl	hydrogen	$-(CH_2)_4-$	2-methoxyethyl
isopropyl	hydrogen	$-(CH_2)_4-$	hydroxymethyl
isopropyl	hydrogen	$-(CH_2)_4-$	2-hydroxyethyl
isopropyl	hydrogen	$-(CH_2)_5-$	methyl
isopropyl	hydrogen	$-(CH_2)_5-$	ethyl
isopropyl	hydrogen	$-(CH_2)_5-$	n-propyl
isopropyl	hydrogen	$-(CH_2)_5-$	n-butyl
isopropyl	hydrogen	$-(CH_2)_5-$	ethoxymethyl
isopropyl	hydrogen	$-(CH_2)_5-$	2-methoxyethyl
isopropyl	hydrogen	$-(CH_2)_5-$	hydroxymethyl
isopropyl	hydrogen	$-(CH_2)_5-$	2-hydroxyethyl
isopropyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	methyl
isopropyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	ethyl
isopropyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	n-propyl
isopropyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	n-butyl
isopropyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
isopropyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	2-methoxyethyl
isopropyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	hydroxymethyl
isopropyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	2-hydroxyethyl
methyl	hydrogen	$-(CH_2)_2-$	methyl
methyl	hydrogen	$-(CH_2)_2-$	ethyl
methyl	hydrogen	$-(CH_2)_2-$	n-propyl
methyl	hydrogen	$-(CH_2)_2-$	n-butyl
methyl	hydrogen	$-(CH_2)_2-$	ethoxymethyl
methyl	hydrogen	$-(CH_2)_2-$	2-methoxyethyl
methyl	hydrogen	$-(CH_2)_2-$	hydroxymethyl
methyl	hydrogen	$-(CH_2)_2-$	2-hydroxyethyl
methyl	hydrogen	$-(CH_2)_3-$	methyl

R_1	R_1'	X'	R_2
methyl	hydrogen	$-(CH_2)_3-$	ethyl
methyl	hydrogen	$-(CH_2)_3-$	n-propyl
methyl	hydrogen	$-(CH_2)_3-$	n-butyl
methyl	hydrogen	$-(CH_2)_3-$	ethoxymethyl
methyl	hydrogen	$-(CH_2)_3-$	2-methoxyethyl
methyl	hydrogen	$-(CH_2)_3-$	hydroxymethyl
methyl	hydrogen	$-(CH_2)_3-$	2-hydroxyethyl
methyl	hydrogen	$-(CH_2)_4-$	methyl
methyl	hydrogen	$-(CH_2)_4-$	ethyl
methyl	hydrogen	$-(CH_2)_4-$	n-propyl
methyl	hydrogen	$-(CH_2)_4-$	n-butyl
methyl	hydrogen	$-(CH_2)_4-$	ethoxymethyl
methyl	hydrogen	$-(CH_2)_4-$	2-methoxyethyl
methyl	hydrogen	$-(CH_2)_4-$	hydroxymethyl
methyl	hydrogen	$-(CH_2)_4-$	2-hydroxyethyl
methyl	hydrogen	$-(CH_2)_5-$	methyl
methyl	hydrogen	$-(CH_2)_5-$	ethyl
methyl	hydrogen	$-(CH_2)_5-$	n-propyl
methyl	hydrogen	$-(CH_2)_5-$	n-butyl
methyl	hydrogen	$-(CH_2)_5-$	ethoxymethyl
methyl	hydrogen	$-(CH_2)_5-$	2-methoxyethyl
methyl	hydrogen	$-(CH_2)_5-$	hydroxymethyl
methyl	hydrogen	$-(CH_2)_5-$	2-hydroxyethyl
methyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	methyl
methyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	ethyl
methyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	n-propyl
methyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	n-butyl
methyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
methyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	2-methoxyethyl
methyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	hydroxymethyl
methyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	2-hydroxyethyl
methyl	methyl	$-(CH_2)_2-$	methyl
methyl	methyl	$-(CH_2)_2-$	ethyl
methyl	methyl	$-(CH_2)_2-$	n-propyl
methyl	methyl	$-(CH_2)_2-$	n-butyl
methyl	methyl	$-(CH_2)_2-$	ethoxymethyl
methyl	methyl	$-(CH_2)_2-$	2-methoxyethyl
methyl	methyl	$-(CH_2)_2-$	hydroxymethyl
methyl	methyl	$-(CH_2)_2-$	2-hydroxyethyl
methyl	methyl	$-(CH_2)_3-$	methyl
methyl	methyl	$-(CH_2)_3-$	ethyl
methyl	methyl	$-(CH_2)_3-$	n-propyl
methyl	methyl	$-(CH_2)_3-$	n-butyl
methyl	methyl	$-(CH_2)_3-$	ethoxymethyl
methyl	methyl	$-(CH_2)_3-$	2-methoxyethyl

R_1	R_1'	X'	R_2
methyl	methyl	$-(CH_2)_3-$	hydroxymethyl
methyl	methyl	$-(CH_2)_3-$	2-hydroxyethyl
methyl	methyl	$-(CH_2)_4-$	methyl
methyl	methyl	$-(CH_2)_4-$	ethyl
methyl	methyl	$-(CH_2)_4-$	n-propyl
methyl	methyl	$-(CH_2)_4-$	n-butyl
methyl	methyl	$-(CH_2)_4-$	ethoxymethyl
methyl	methyl	$-(CH_2)_4-$	2-methoxyethyl
methyl	methyl	$-(CH_2)_4-$	hydroxymethyl
methyl	methyl	$-(CH_2)_4-$	2-hydroxyethyl
methyl	methyl	$-(CH_2)_5-$	methyl
methyl	methyl	$-(CH_2)_5-$	ethyl
methyl	methyl	$-(CH_2)_5-$	n-propyl
methyl	methyl	$-(CH_2)_5-$	n-butyl
methyl	methyl	$-(CH_2)_5-$	ethoxymethyl
methyl	methyl	$-(CH_2)_5-$	2-methoxyethyl
methyl	methyl	$-(CH_2)_5-$	hydroxymethyl
methyl	methyl	$-(CH_2)_5-$	2-hydroxyethyl
methyl	methyl	$-CH_2C(CH_3)_2CH_2-$	methyl
methyl	methyl	$-CH_2C(CH_3)_2CH_2-$	ethyl
methyl	methyl	$-CH_2C(CH_3)_2CH_2-$	n-propyl
methyl	methyl	$-CH_2C(CH_3)_2CH_2-$	n-butyl
methyl	methyl	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
methyl	methyl	$-CH_2C(CH_3)_2CH_2-$	2-methoxyethyl
methyl	methyl	$-CH_2C(CH_3)_2CH_2-$	hydroxymethyl
methyl	methyl	$-CH_2C(CH_3)_2CH_2-$	2-hydroxyethyl
morpholine		$-(CH_2)_2-$	methyl
morpholine		$-(CH_2)_2-$	ethyl
morpholine		$-(CH_2)_2-$	n-propyl
morpholine		$-(CH_2)_2-$	n-butyl
morpholine		$-(CH_2)_2-$	ethoxymethyl
morpholine		$-(CH_2)_2-$	2-methoxyethyl
morpholine		$-(CH_2)_2-$	hydroxymethyl
morpholine		$-(CH_2)_2-$	2-hydroxyethyl
morpholine		$-(CH_2)_3-$	methyl
morpholine		$-(CH_2)_3-$	ethyl
morpholine		$-(CH_2)_3-$	n-propyl
morpholine		$-(CH_2)_3-$	n-butyl
morpholine		$-(CH_2)_3-$	ethoxymethyl
morpholine		$-(CH_2)_3-$	2-methoxyethyl
morpholine		$-(CH_2)_3-$	hydroxymethyl
morpholine		$-(CH_2)_3-$	2-hydroxyethyl
morpholine		$-(CH_2)_4-$	methyl
morpholine		$-(CH_2)_4-$	ethyl
morpholine		$-(CH_2)_4-$	n-propyl

R_1	R_1'	X'	R_2
morpholine		$-(CH_2)_4-$	n-butyl
morpholine		$-(CH_2)_4-$	ethoxymethyl
morpholine		$-(CH_2)_4-$	2-methoxyethyl
morpholine		$-(CH_2)_4-$	hydroxymethyl
morpholine		$-(CH_2)_4-$	2-hydroxyethyl
morpholine		$-(CH_2)_5-$	methyl
morpholine		$-(CH_2)_5-$	ethyl
morpholine		$-(CH_2)_5-$	n-propyl
morpholine		$-(CH_2)_5-$	n-butyl
morpholine		$-(CH_2)_5-$	ethoxymethyl
morpholine		$-(CH_2)_5-$	2-methoxyethyl
morpholine		$-(CH_2)_5-$	hydroxymethyl
morpholine		$-(CH_2)_5-$	2-hydroxyethyl
morpholine		$-CH_2C(CH_3)_2CH_2-$	methyl
morpholine		$-CH_2C(CH_3)_2CH_2-$	ethyl
morpholine		$-CH_2C(CH_3)_2CH_2-$	n-propyl
morpholine		$-CH_2C(CH_3)_2CH_2-$	n-butyl
morpholine		$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
morpholine		$-CH_2C(CH_3)_2CH_2-$	2-methoxyethyl

CYTOKINE INDUCTION IN HUMAN CELLS

Compounds of the invention have been found to modulate cytokine biosynthesis by inducing the production of interferon α and/or tumor necrosis factor α when tested using the method described below.

An in vitro human blood cell system is used to assess cytokine induction. Activity is based on the measurement of interferon and tumor necrosis factor (α) (IFN and TNF, respectively) secreted into culture media as described by Testerman et. al. in "Cytokine Induction by the Immunomodulators Imiquimod and S-27609", Journal of Leukocyte Biology, 58, 365-372 (September, 1995).

Blood Cell Preparation for Culture

Whole blood from healthy human donors is collected by venipuncture into EDTA vacutainer tubes. Peripheral blood mononuclear cells (PBMC) are separated from whole blood by density gradient centrifugation using HISTOPAQUE-1077. Blood is diluted 1:1 with Dulbecco's Phosphate Buffered Saline (DPBS) or Hank's Balanced Salts Solution (HBSS). The PBMC layer is collected and washed twice with DPBS or HBSS and resuspended at 4 x 10^6 cells/mL in RPMI complete. The PBMC suspension is added to 48

well flat bottom sterile tissue culture plates (Costar, Cambridge, MA or Becton Dickinson Labware, Lincoln Park, NJ) containing an equal volume of RPMI complete media containing test compound.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. The compounds are generally tested at concentrations ranging from 30-0.014 μM.

Incubation

The solution of test compound is added at 60 μM to the first well containing RPMI complete and serial 3 fold dilutions are made in the wells. The PBMC suspension is then added to the wells in an equal volume, bringing the test compound concentrations to the desired range (30-0.014 μM). The final concentration of PBMC suspension is 2×10^6 cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.

Separation

Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (approximately 200 x g) at 4°C. The cell-free culture supernatant is removed with a sterile polypropylene pipet and transferred to sterile polypropylene tubes. Samples are maintained at –30 to -70°C until analysis. The samples are analyzed for interferon (α) by ELISA and for tumor necrosis factor (α) by ELISA or IGEN Assay.

Interferon (α) and Tumor Necrosis Factor (α) Analysis by ELISA

Interferon (α) concentration is determined by ELISA using a Human Multi-Species kit from PBL Biomedical Laboratories, New Brunswick, NJ. Results are expressed in pg/mL.

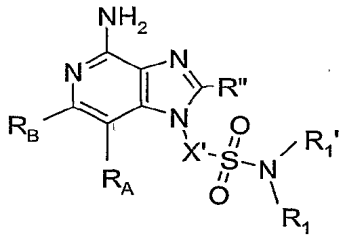
Tumor necrosis factor (α) (TNF) concentration is determined using ELISA kits available from Biosource International, Camarillo, CA. Alternately, the TNF concentration can be determined by ORIGEN M-Series Immunoassay and read on an

IGEN M-8 analyzer from IGEN International, Gaithersburg, MD. The immunoassay uses a human TNF capture and detection antibody pair from Biosource International, Camarillo, CA. Results are expressed in pg/mL.

The complete disclosures of the patents, patent documents, and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. It should be understood that this invention is not intended to be unduly limited by the illustrative embodiments and examples set forth herein and that such examples and embodiments are presented by way of example only with the scope of the invention intended to be limited only by the claims set forth herein as follows.

WHAT IS CLAIMED IS:

1. A compound of the formula (I):



(I)

wherein:

X' is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene, and -CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1 and R_1' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

haloalkoxy,

halogen,

cyano,

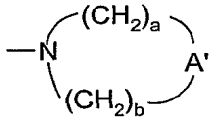
nitro,

arylsulfonyl,

alkylsulfonyl, and

$-N(R_9)_2$,

or R_1 and R_1' can join together to form a ring of the formula:



;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, $-N(R_4)-$, and $-N(Q-R_4)-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkylenyloxy, heteroaryl, heteroaryloxy, heteroarylalkylenyloxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkylenyloxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_6 is selected from the group consisting of =O and =S;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R'' is hydrogen or a non-interfering substituent;

R_A and R_B are independently selected from the group consisting of:

hydrogen,
halogen,
alkyl,
alkenyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

or R_A and R_B taken together form either a fused aryl ring that is unsubstituted or substituted by one or more R_a groups, or a fused 5 to 7 membered saturated ring that is unsubstituted or substituted by one or more R_c groups;

or R_A and R_B taken together form a fused heteroaryl or 5 to 7 membered saturated ring, containing one heteroatom selected from the group consisting of N and S, wherein the heteroaryl ring is unsubstituted or substituted by one or more R_b groups, and the 5 to 7 membered saturated ring is unsubstituted or substituted by one or more R_c groups;

R_a is selected from the group consisting of:
fluoro,
alkyl,
haloalkyl,
alkoxy, and
$-N(R_9)_2$;

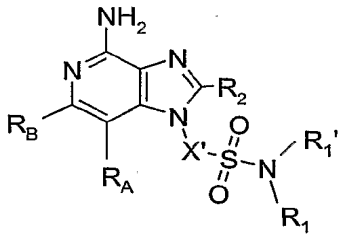
R_b is selected from the group consisting of:
halogen,
hydroxy,
alkyl,
alkenyl,
haloalkyl,
alkoxy, and
$-N(R_9)_2$; and

R_c is selected from the group consisting of:
halogen,
hydroxy,
alkyl,

alkenyl,
haloalkyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

or a pharmaceutically acceptable salt thereof.

2. A compound of the formula (Ia):



(Ia)

wherein:

X' is selected from the group consisting of $-CH(R_9)-$, $-CH(R_9)$-alkylene, and $-CH(R_9)$-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

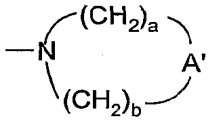
R_1 and R_1' are independently selected from the group consisting of:

hydrogen,
alkyl,
alkenyl,
aryl,
arylalkylenyl,
heteroaryl,
heteroarylalkylenyl,
heterocyclyl,
heterocyclylalkylenyl, and
alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
haloalkoxy,
halogen,
cyano,
nitro,
arylsulfonyl,
alkylsulfonyl, and
$-N(R_9)_2$,

or R_1 and R_1' can join together to form a ring of the formula:



;

R_2 is selected from the group consisting of:

$-R_4$,
$-X-R_4$,
$-X-Y-R_4$, and
$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

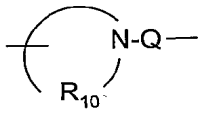
-O-,
$-S(O)_{0-2}-$,
$-S(O)_2-N(R_8)-$,
$-C(R_6)-$,
$-C(R_6)-O-$,
$-O-C(R_6)-$,
-O-C(O)-O-,

-N(R_8)-Q-,

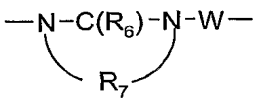
-C(R_6)-N(R_8)-,

-O-C(R_6)-N(R_8)-,

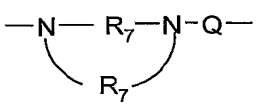
-C(R_6)-N(OR_9)-,



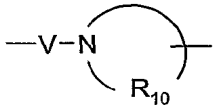
,



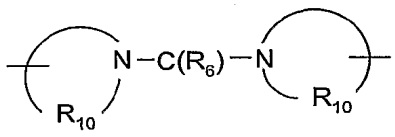
,



,



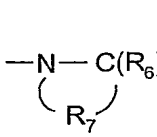
, and



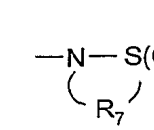
;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkylenyloxy, heteroaryl, heteroaryloxy, heteroarylalkylenyloxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkylenyloxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

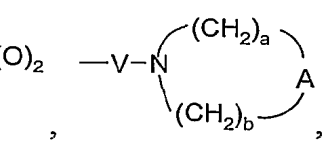
R_5 is selected from the group consisting of:



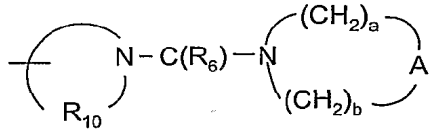
,



,



, and



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$,$-N(R_4)-$, and $-N(Q-R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_A and R_B are independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

or R_A and R_B taken together form either a fused aryl ring that is unsubstituted or substituted by one or more R_a groups, or a fused 5 to 7 membered saturated ring that is unsubstituted or substituted by one or more R_c groups;

or R_A and R_B taken together form a fused heteroaryl or 5 to 7 membered saturated ring, containing one heteroatom selected from the group consisting of N and S, wherein the heteroaryl ring is unsubstituted or substituted by one or more R_b groups, and the 5 to 7 membered saturated ring is unsubstituted or substituted by one or more R_c groups;

R_a is selected from the group consisting of:

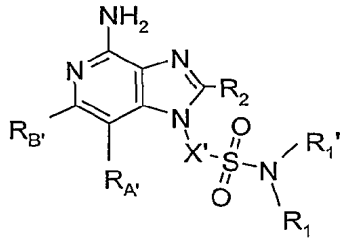
fluoro,
alkyl,
haloalkyl,
alkoxy, and
$-N(R_9)_2$;

R_b is selected from the group consisting of:
halogen,
hydroxy,
alkyl,
alkenyl,
haloalkyl,
alkoxy, and
$-N(R_9)_2$; and

R_c is selected from the group consisting of:
halogen,
hydroxy,
alkyl,
alkenyl,
haloalkyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

or a pharmaceutically acceptable salt thereof.

3. A compound of the formula (Ib):



Ib

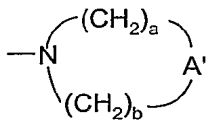
wherein:

X' is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene, and -CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1 and R_1' are independently selected from the group consisting of:

hydrogen,
alkyl,
alkenyl,
aryl,
arylalkylenyl,
heteroaryl,
heteroarylalkylenyl,
heterocyclyl,
heterocyclylalkylenyl, and
alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:
hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
haloalkoxy,
halogen,
cyano,
nitro,
arylsulfonyl,
alkylsulfonyl, and
-N(R_9)$_2$,

or R_1 and R_1' can join together to form a ring of the formula:



;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-O-$,

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

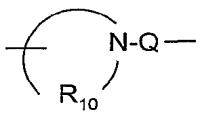
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

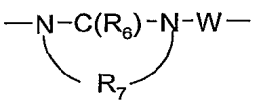
$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

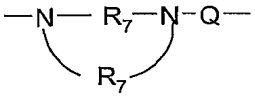
$-C(R_6)-N(OR_9)-$,



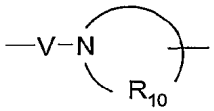
,



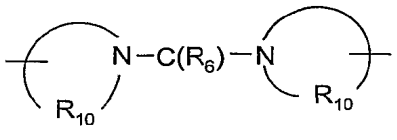
,



,



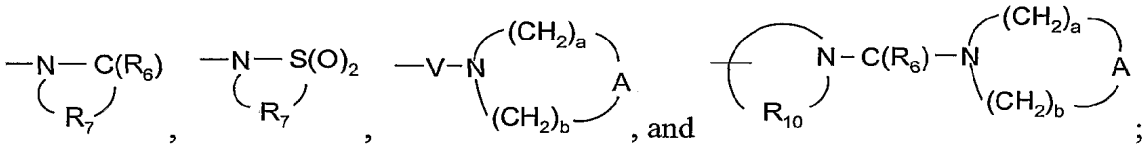
, and



;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkylenyloxy, heteroaryl, heteroaryloxy, heteroarylalkylenyloxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkylenyloxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$,$-N(R_4)-$, and $-N(Q-R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and -$S(O)_2$-;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7; and

R_A' and R_B' are independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

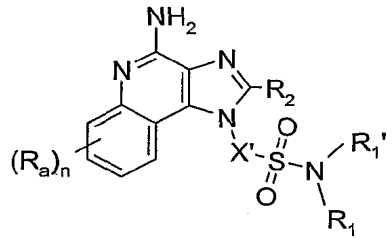
alkoxy,

alkylthio, and

-$N(R_9)_2$;

or a pharmaceutically acceptable salt thereof.

4. A compound of the formula (II):



(II)

wherein:

X' is selected from the group consisting of -$CH(R_9)$-, -$CH(R_9)$-alkylene, and -$CH(R_9)$-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1 and R_1' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

haloalkoxy,

halogen,

cyano,

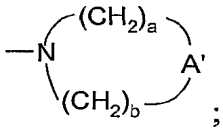
nitro,

arylsulfonyl,

alkylsulfonyl, and

$-N(R_9)_2$,

or R_1 and R_1' can join together to form a ring of the formula:



;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_8)$-,

-$C(R_6)$-,

-$C(R_6)$-O-,

-O-$C(R_6)$-,

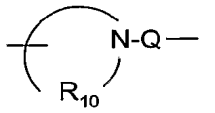
-O-C(O)-O-,

-$N(R_8)$-Q-,

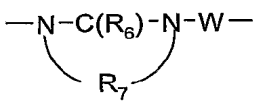
-$C(R_6)$-$N(R_8)$-,

-O-$C(R_6)$-$N(R_8)$-,

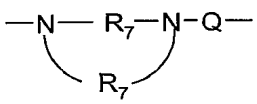
-$C(R_6)$-$N(OR_9)$-,



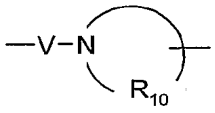
,



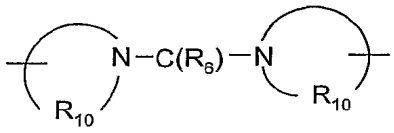
,



,



, and

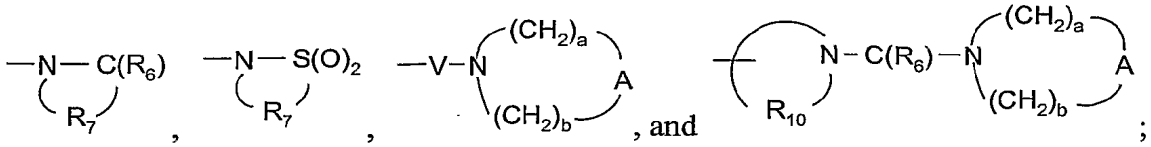


;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkylenyloxy, heteroaryl, heteroaryloxy, heteroarylalkylenyloxy, heterocyclyl, amino, alkylamino, dialkylamino,

(dialkylamino)alkylenyloxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$,$-N(R_4)-$, and $-N(Q-R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

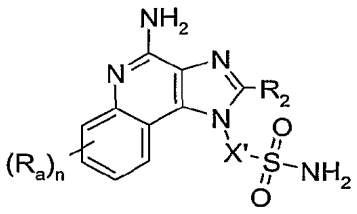
a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_a is selected from the group consisting of fluoro, alkyl, haloalkyl, alkoxy, and $-N(R_9)_2$; and

n is 0 to 4;

or a pharmaceutically acceptable salt thereof.

5. A compound of the formula (IIa):



(IIa)

wherein:

X' is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene, and -CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_2 is selected from the group consisting of:

-R_4,

-X-R_4,

-X-Y-R_4, and

-X- R_5;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_8)$-,

-$C(R_6)$-,

-$C(R_6)$-O-,

-O-$C(R_6)$-,

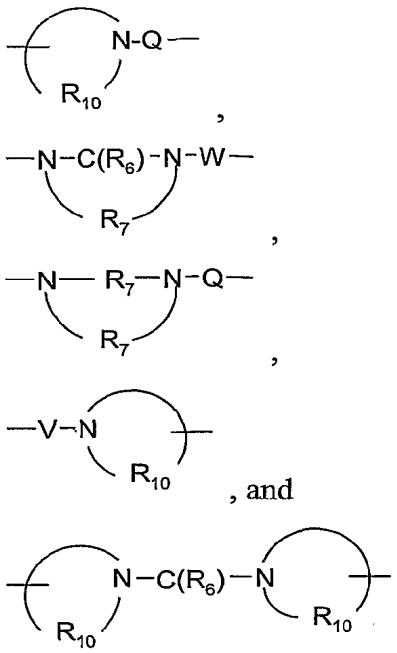
-O-C(O)-O-,

-$N(R_8)$-Q-,

-$C(R_6)$-$N(R_8)$-,

-O-$C(R_6)$-$N(R_8)$-,

-$C(R_6)$-$N(OR_9)$-,

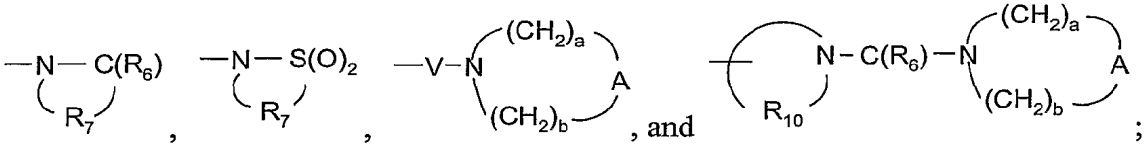


, and

;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkylenyloxy, heteroaryl, heteroaryloxy, heteroarylalkylenyloxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkylenyloxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



, , , and ;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

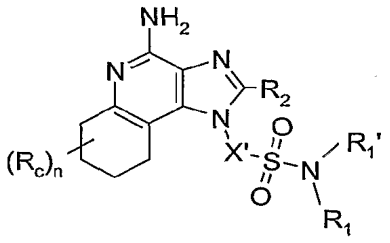
a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_a is selected from the group consisting of fluoro, alkyl, haloalkyl, alkoxy, and $-N(R_9)_2$; and

n is 0 to 4;

or a pharmaceutically acceptable salt thereof.

6. A compound of the formula (III):



(III)

wherein:

X' is selected from the group consisting of $-CH(R_9)-$, $-CH(R_9)$-alkylene, and $-CH(R_9)$-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1 and R_1' are independently selected from the group consisting of:

hydrogen,

alkyl,

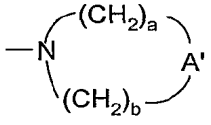
alkenyl,

aryl,

arylalkylenyl,

heteroaryl,
heteroarylalkylenyl,
heterocyclyl,
heterocyclylalkylenyl, and
alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:
hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
haloalkoxy,
halogen,
cyano,
nitro,
arylsulfonyl,
alkylsulfonyl, and
$-N(R_9)_2$,

or R_1 and R_1' can join together to form a ring of the formula:



;

R_2 is selected from the group consisting of:
$-R_4$,
$-X-R_4$,
$-X-Y-R_4$, and
$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_8)$-,

-$C(R_6)$-,

-$C(R_6)$-O-,

-O-$C(R_6)$-,

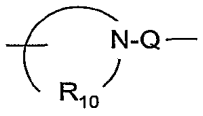
-O-C(O)-O-,

-$N(R_8)$-Q-,

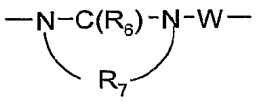
-$C(R_6)$-$N(R_8)$-,

-O-$C(R_6)$-$N(R_8)$-,

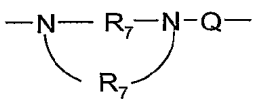
-$C(R_6)$-$N(OR_9)$-,



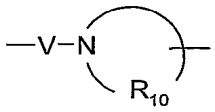
,



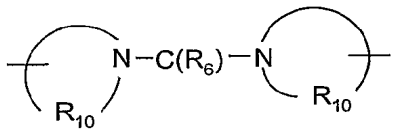
,



,



, and

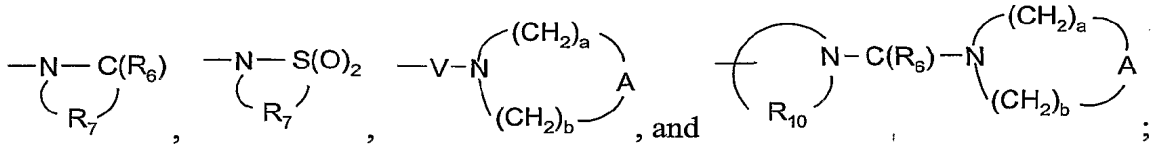


;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen,

nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkylenyloxy, heteroaryl, heteroaryloxy, heteroarylalkylenyloxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkylenyloxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$,$-N(R_4)-$, and $-N(Q-R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

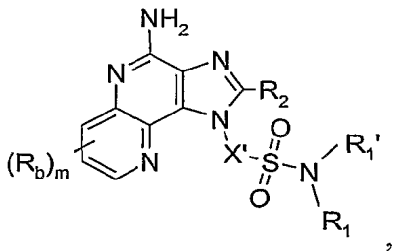
a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_c is selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; and

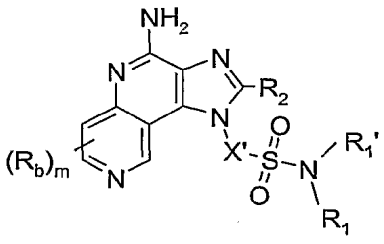
n is 0 to 4;

or a pharmaceutically acceptable salt thereof.

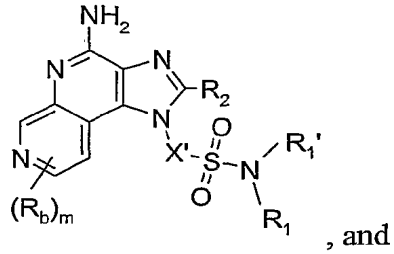
7. A compound selected from the group consisting of formulas (IV, V, VI, and VII):



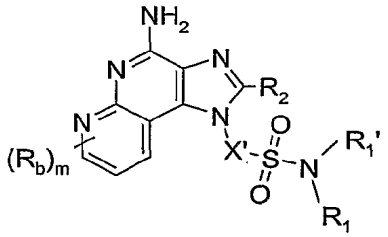
(IV)



(V)



(VI), and



(VII)

wherein:

X' is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene, and -CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1 and R_1' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

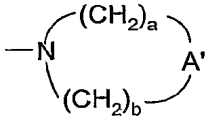
heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
haloalkoxy,
halogen,
cyano,
nitro,
arylsulfonyl,
alkylsulfonyl, and
$-N(R_9)_2$,

or R_1 and R_1' can join together to form a ring of the formula:



;

R_2 is selected from the group consisting of:

$-R_4$,
$-X-R_4$,
$-X-Y-R_4$, and
$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

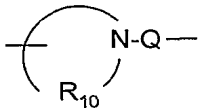
-O-,
$-S(O)_{0-2}-$,
$-S(O)_2-N(R_8)-$,
$-C(R_6)-$,
$-C(R_6)-O-$,
$-O-C(R_6)-$,
-O-C(O)-O-,

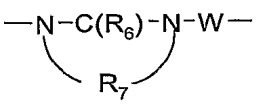
$-N(R_8)-Q-$,

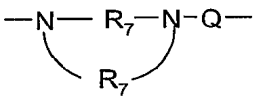
$-C(R_6)-N(R_8)-$,

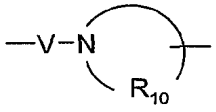
$-O-C(R_6)-N(R_8)-$,

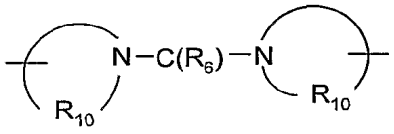
$-C(R_6)-N(OR_9)-$,


,


,

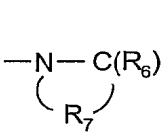

,

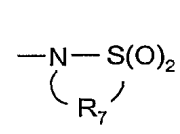

, and

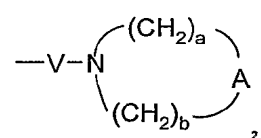

;

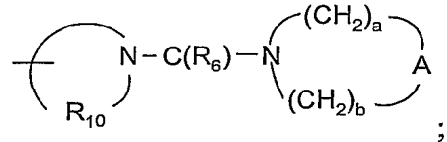
R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkylenyloxy, heteroaryl, heteroaryloxy, heteroarylalkylenyloxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkylenyloxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:


,


,


, and


;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$,$-N(R_4)-$, and $-N(Q-R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

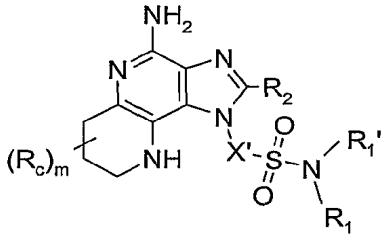
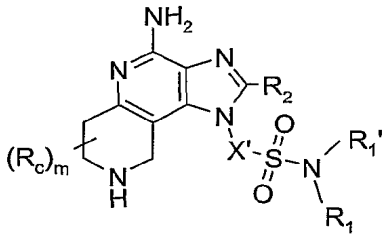
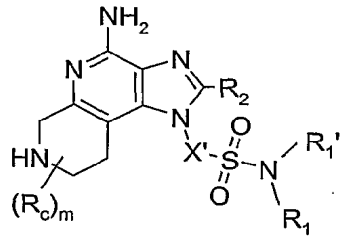
a and b are independently integers from 1 to 6 with the proviso that $a + b \leq 7$;

R_b is selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, haloalkyl, alkoxy, and $-N(R_9)_2$; and

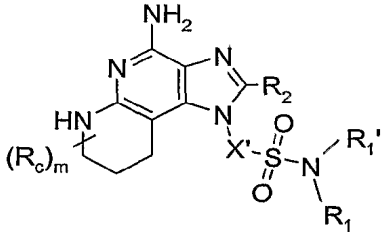
m is 0 to 3;

or a pharmaceutically acceptable salt thereof.

8. A compound selected from the group consisting of formulas (VIII, IX, X, and XI):




, and

(VIII) (IX) (X)



(XI)

wherein:

X' is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene, and -CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1 and R_1' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

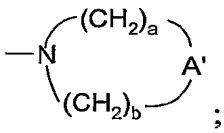
hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,
alkoxy,
haloalkoxy,
halogen,
cyano,
nitro,
arylsulfonyl,
alkylsulfonyl, and
$-N(R_9)_2$,

or R_1 and R_1' can join together to form a ring of the formula:



;

R_2 is selected from the group consisting of:

$-R_4$,
$-X-R_4$,
$-X-Y-R_4$, and
$-X-R_5$;

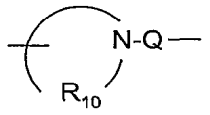
X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

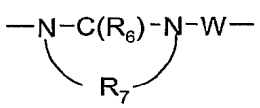
Y is selected from the group consisting of:

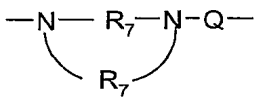
-O-,
$-S(O)_{0-2}-$,
$-S(O)_2-N(R_8)-$,
$-C(R_6)-$,
$-C(R_6)-O-$,
$-O-C(R_6)-$,
-O-C(O)-O-,
$-N(R_8)-Q-$,
$-C(R_6)-N(R_8)-$,

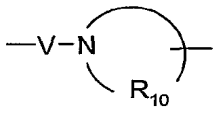
-O-C(R_6)-N(R_8)-,

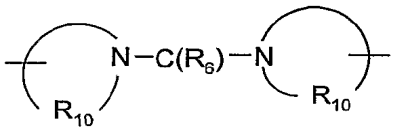
-C(R_6)-N(OR_9)-,


,


,

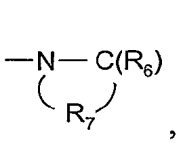

,

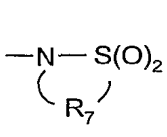

, and

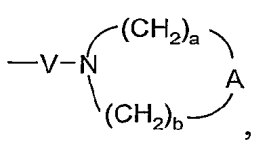

;

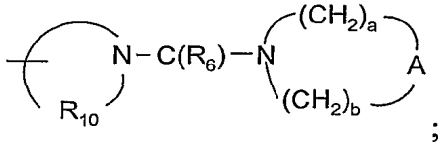
R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkylenyloxy, heteroaryl, heteroaryloxy, heteroarylalkylenyloxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkylenyloxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:


,


,


, and


;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$,$-N(R_4)-$, and $-N(Q-R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7;

R_c is selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; and

m is 0 to 3;

or a pharmaceutically acceptable salt thereof.

9. The compound or salt of claim 1 or claim 2 wherein R_A and R_B are independently selected from the group consisting of hydrogen and C_{1-4} alkyl.

10. The compound or salt of claim 3 wherein $R_{A'}$ and $R_{B'}$ are independently selected from the group consisting of hydrogen and C_{1-4} alkyl.

11. The compound or salt of claim 7 or claim 8 wherein m is 0.

12. The compound or salt of any one of claims 4, 5, or 6 wherein n is 0.

13. The compound or salt of any one of claims 1 through 4, 6 through 11, or claim 12 as dependent on claim 4 or claim 6, wherein R_1 and R_1' are independently selected from the group consisting of:

hydrogen,
alkyl,
alkenyl,
aryl,
arylalkylenyl,
heteroaryl,
heteroarylalkylenyl,
heterocyclyl,
heterocyclylalkylenyl, and
alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:
hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
haloalkoxy,
halogen,
cyano,
nitro,
arylsulfonyl,
alkylsulfonyl, and
$-N(R_9)_2$.

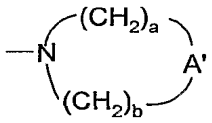
14. The compound or salt of claim 13 wherein R_1' is hydrogen or alkyl, and R_1 is selected from the group consisting of hydrogen, alkyl, aryl, substituted aryl, arylalkylenyl, substituted arylalkylenyl, and heteroaryl.

15. The compound or salt of claim 13 wherein R_1' is hydrogen or methyl, and R_1 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, cyclohexyl,

phenyl, 4-methoxyphenyl, benzyl, 4-methoxybenzyl, 2-pyridyl, 3-pyridyl, 4-chlorophenyl, and 4-fluorophenyl.

16. The compound or salt of claim 15 wherein R_1 and R_1' are both hydrogen.

17. The compound or salt of any one of claims 1 through 4, 6 through 11, or claim 12 as dependent on claim 4 or claim 6, wherein R_1 and R_1' join together to form a ring of the formula:



wherein A' is selected from the group consisting of -O-, $-CH_2-$, $-N(R_4)-$, and $-N(Q-R_4)-$.

18. The compound or salt of claim 17 wherein R_1 and R_1' join together to form a morpholine ring.

19. The compound or salt of any one of claims 2 through 8; claim 9 as dependent on claim 2; claims 10 through 12; or claims 13 through 18 as dependent on claims 2 through 4, claims 6 through 11, or claim 12 as dependent on claim 4 or claim 6; wherein R_2 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, and -X-R_4 and -X-Y-R_4, wherein X is C_{1-2} alkyl; Y is $-S(O)_{0-2}-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-$, $-C(R_6)-O-$, $-O-C(R_6)-$, -O-C(O)-O-, $-N(R_8)-Q-$, $-C(R_6)-N(R_8)-$, $-O-C(R_6)-N(R_8)-$, or $-C(R_6)-N(OR_9)-$; and R_4 is alkyl.

20. The compound or salt of claim 19 wherein R_2 is selected from the group consisting of hydrogen, C_{1-4} alkyl, C_{1-4} alkyl-O-C_{1-4} alkylenyl, and HO-C_{1-3} alkylenyl.

21. The compound or salt of claim 20 wherein R_2 is selected from the group consisting of hydrogen, methyl, ethyl, *n*-propyl, *n*-butyl, hydroxymethyl, 2-hydroxyethyl, ethoxymethyl, and 2-methoxyethyl.

22. The compound or salt of any one of claims 1 through 21 wherein X' is

$-(CH_2)_{2-4}-O-(CH_2)_{2-4}-$.

23. The compound or salt of any one of claims 1 through 21 wherein X' is $-(CH_2)_{1-7}-$.

24. The compound or salt of any one of claims 1 through 21 wherein X' is $-(CH_2)-C(CH_3)_2-$.

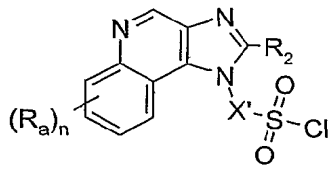
25. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of any one of claims 1 through 24 in combination with a pharmaceutically acceptable carrier.

26. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of any one of claims 1 through 24 or a pharmaceutical composition of claim 25 to the animal.

27. A method of treating a viral disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of any one of claims 1 through 24 or a pharmaceutical composition of claim 25 to the animal.

28. A method of treating a neoplastic disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of any one of claims 1 through 24 or a pharmaceutical composition of claim 25 to the animal.

29. A compound of the formula (XII):



(XII)

wherein:

X' is selected from the group consisting of $-CH(R_9)-$, $-CH(R_9)$-alkylene, and

-CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_2 is selected from the group consisting of:

-R_4,

-X-R_4,

-X-Y-R_4, and

-X- R_5;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_8)$-,

-$C(R_6)$-,

-$C(R_6)$-O-,

-O-$C(R_6)$-,

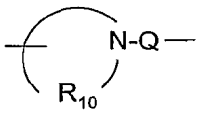
-O-C(O)-O-,

-$N(R_8)$-Q-,

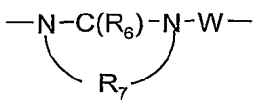
-$C(R_6)$-$N(R_8)$-,

-O-$C(R_6)$-$N(R_8)$-,

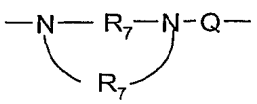
-$C(R_6)$-$N(OR_9)$-,



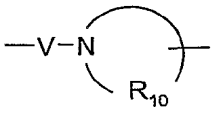
,

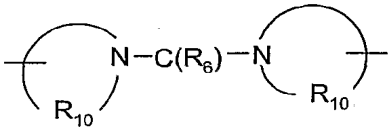


,



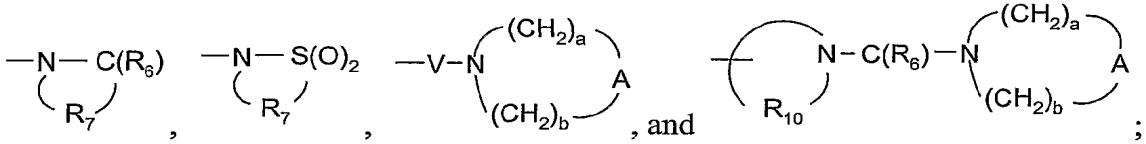
,


, and


;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkylenyloxy, heteroaryl, heteroaryloxy, heteroarylalkylenyloxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkylenyloxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:


;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and

$-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

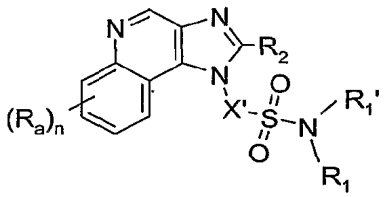
a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_a is selected from the group consisting of fluoro, alkyl, haloalkyl, alkoxy, and $-N(R_9)_2$; and

n is 0 to 4;

or a pharmaceutically acceptable salt thereof.

30. A compound of the formula (XIII):



(XIII)

wherein:

X' is selected from the group consisting of $-CH(R_9)-$, $-CH(R_9)$-alkylene, and $-CH(R_9)$-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1 and R_1' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

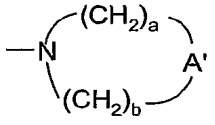
heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
haloalkoxy,
halogen,
cyano,
nitro,
arylsulfonyl,
alkylsulfonyl, and
$-N(R_9)_2$,

or R_1 and R_1' can join together to form a ring of the formula:



;

R_2 is selected from the group consisting of:

$-R_4$,
$-X-R_4$,
$-X-Y-R_4$, and
$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

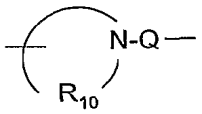
-O-,
$-S(O)_{0-2}-$,
$-S(O)_2-N(R_8)-$,
$-C(R_6)-$,
$-C(R_6)-O-$,
$-O-C(R_6)-$,
-O-C(O)-O-,

$-N(R_8)-Q-$,

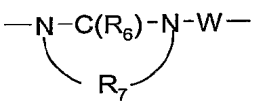
$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

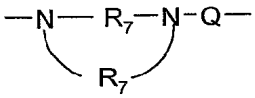
$-C(R_6)-N(OR_9)-$,



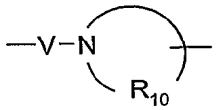
,



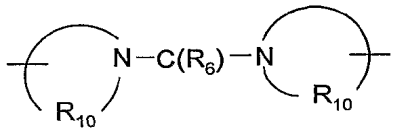
,



,



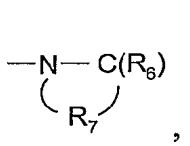
, and



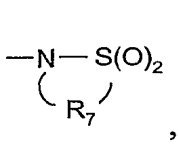
;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkylenyloxy, heteroaryl, heteroaryloxy, heteroarylalkylenyloxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkylenyloxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

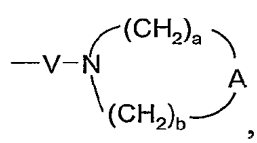
R_5 is selected from the group consisting of:



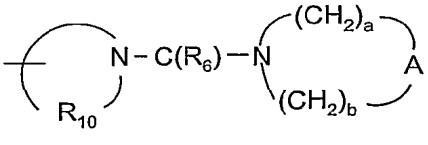
,



,



, and



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$,$-N(R_4)-$, and $-N(Q-R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

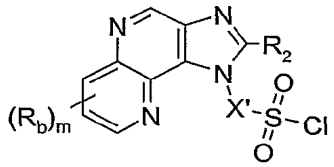
a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_a is selected from the group consisting of fluoro, alkyl, haloalkyl, alkoxy, and $-N(R_9)_2$; and

n is 0 to 4;

or a pharmaceutically acceptable salt thereof.

31. A compound of the formula (XIV):



(XIV)

wherein:

X' is selected from the group consisting of $-CH(R_9)-$, $-CH(R_9)$-alkylene, and $-CH(R_9)$-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-O-$,

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

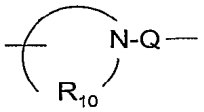
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

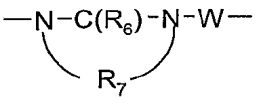
$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

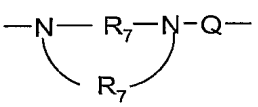
$-C(R_6)-N(OR_9)-$,



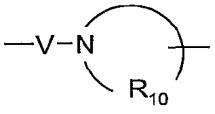
,



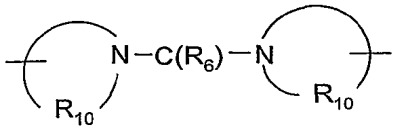
,



,



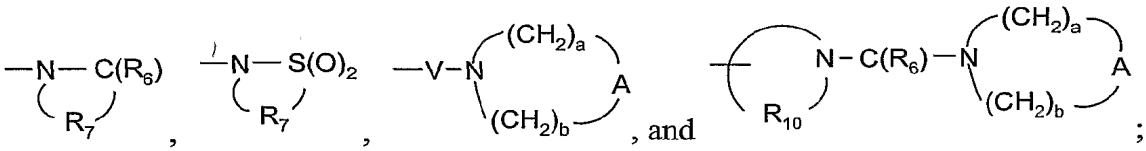
, and



;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkylenyloxy, heteroaryl, heteroaryloxy, heteroarylalkylenyloxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkylenyloxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

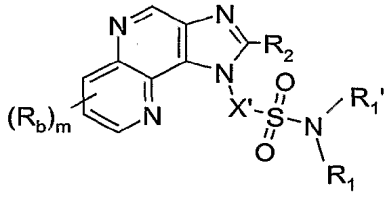
a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_b is selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, haloalkyl, alkoxy, and $-N(R_9)_2$; and

m is 0 to 3;

or a pharmaceutically acceptable salt thereof.

32. A compound of the formula (XV):



(XV)

wherein:

X' is selected from the group consisting of $-CH(R_9)-$, $-CH(R_9)$-alkylene, and $-CH(R_9)$-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1 and R_1' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

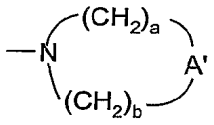
alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,
haloalkoxy,
halogen,
cyano,
nitro,
arylsulfonyl,
alkylsulfonyl, and
$-N(R_9)_2$,

or R_1 and R_1' can join together to form a ring of the formula:



;

R_2 is selected from the group consisting of:

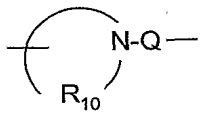
$-R_4$,
$-X-R_4$,
$-X-Y-R_4$, and
$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

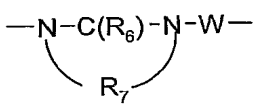
Y is selected from the group consisting of:

-O-,
$-S(O)_{0-2}-$,
$-S(O)_2-N(R_8)-$,
$-C(R_6)-$,
$-C(R_6)-O-$,
$-O-C(R_6)-$,
-O-C(O)-O-,
$-N(R_8)-Q-$,
$-C(R_6)-N(R_8)-$,
$-O-C(R_6)-N(R_8)-$,

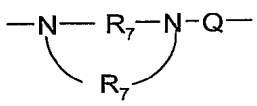
-C(R_6)-N(OR_9)-,



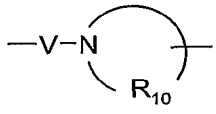
,



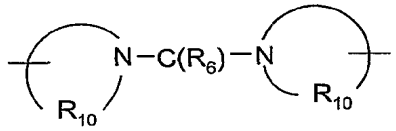
,



,



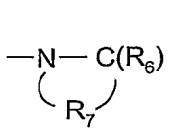
, and



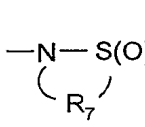
;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkylenyloxy, heteroaryl, heteroaryloxy, heteroarylalkylenyloxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkylenyloxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

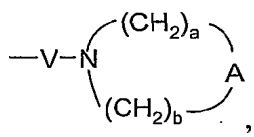
R_5 is selected from the group consisting of:



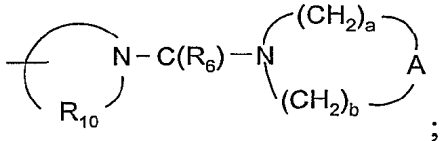
,



,



, and



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$,$-N(R_4)-$, and $-N(Q-R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

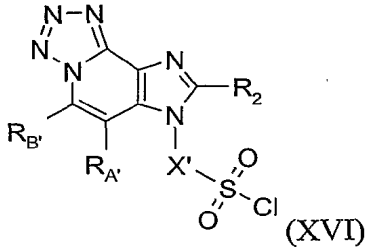
a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_b is selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, haloalkyl, alkoxy, and $-N(R_9)_2$; and

m is 0 to 3;

or a pharmaceutically acceptable salt thereof.

33. A compound of the formula (XVI):



(XVI)

wherein:

X' is selected from the group consisting of $-CH(R_9)-$, $-CH(R_9)$-alkylene, and $-CH(R_9)$-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

-X-Y-R_4, and

-X- R_5;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_8)$-,

-$C(R_6)$-,

-$C(R_6)$-O-,

-O-$C(R_6)$-,

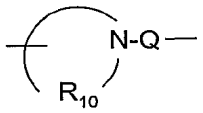
-O-C(O)-O-,

-$N(R_8)$-Q-,

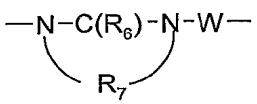
-$C(R_6)$-$N(R_8)$-,

-O-$C(R_6)$-$N(R_8)$-,

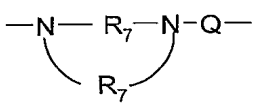
-$C(R_6)$-$N(OR_9)$-,



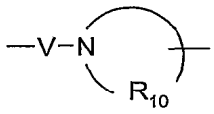
,



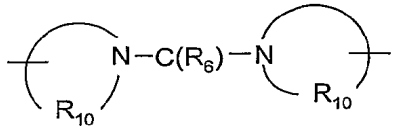
,



,



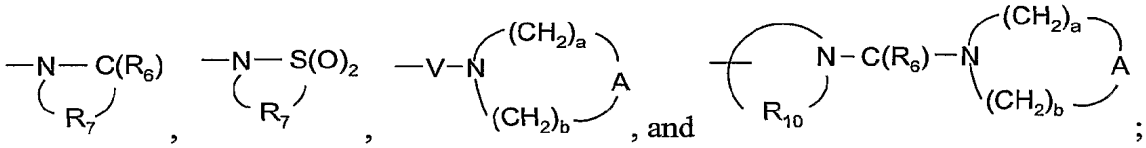
, and



;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkylenyloxy, heteroaryl, heteroaryloxy, heteroarylalkylenyloxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkylenyloxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

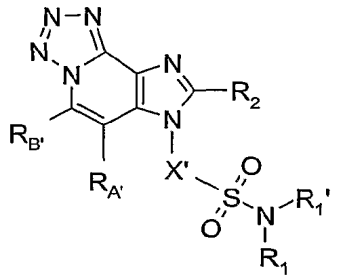
W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7; and

$R_{A'}$ and $R_{B'}$ are independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$;

or a pharmaceutically acceptable salt thereof.

34. A compound of the formula (XVII):



(XVII)

wherein:

X' is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene, and -CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1 and R_1' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

haloalkoxy,

halogen,

cyano,

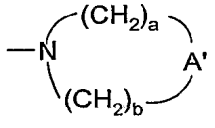
nitro,

arylsulfonyl,

alkylsulfonyl, and

$-N(R_9)_2$,

or R_1 and R_1' can join together to form a ring of the formula:



;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

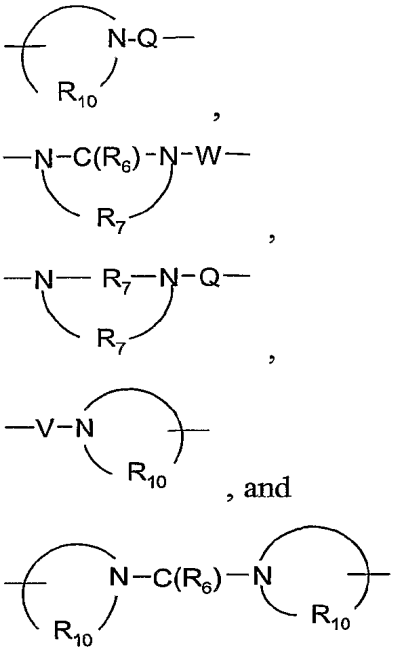
-O-C(O)-O-,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

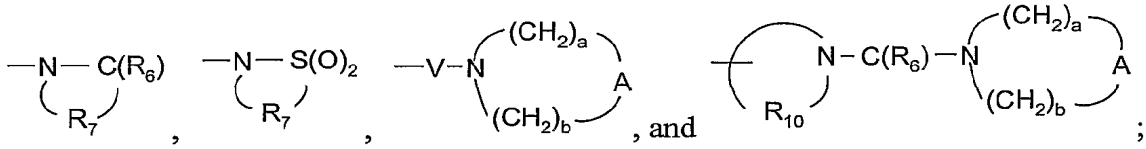
$-C(R_6)-N(OR_9)-$,



, and ;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkylenyloxy, heteroaryl, heteroaryloxy, heteroarylalkylenyloxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkylenyloxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



, , , and ;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$,$-N(R_4)-$, and

$-N(Q-R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_A, and R_B, are independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$;

or a pharmaceutically acceptable salt thereof.